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Low-level exposure to arsenic in drinking water and incidence rate of stroke: A cohort study in Denmark

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ABSTRACT

Introduction: High arsenic concentration in drinking water is associated with a higher incidence rate of stroke, but only few studies have investigated an association with arsenic in drinking water at low concentration (< 50 μg/L).

Objective: To examine if arsenic in drinking water at low concentration was associated with higher incidence rate of stroke in Denmark.

Methods: A total of 57,053 individuals from the Danish Diet, Cancer, and Health cohort was included in the study (enrolment in 1993–1997, age 50–64 years), of which 2195 individuals had incident stroke between enrolment and November 2009. Individuals were enrolled in two major cities (Copenhagen and Aarhus). Residential addresses in the period 1973–2009 were geocoded and arsenic concentration in drinking water at each address was estimated by linking addresses with water supply areas. Associations between arsenic concentration and incidence rate of stroke were analysed using a generalized linear model with a Poisson distribution. Incidence rate ratios (IRR) were adjusted for differences in age, sex, calendar-year, lifestyle factors, and educational level.

Results: Median arsenic concentration in drinking water was 0.7 μg/L at enrolment addresses (range: 0.03 to 25 μg/L), with highest concentrations in the Aarhus area. The adjusted IRRs were 1.17 (95% CI: 1.04–1.32) for the highest arsenic quartile (1.93–25.3 μg/L) when compared with the lowest quartile (0.049–0.57 μg/L), but the highest IRR was seen in the second quartile (0.57–0.76 μg/L) (IRR = 1.21; 95% CI: 1.07–1.36). The highest IRR in the upper quartile was seen in the Aarhus area (IRR = 1.79; 95% CI: 1.41–2.26). Having ever been exposed to10 μg/L or more arsenic in drinking water resulted in an IRR at 1.44 (95% CI: 1.00–2.08) for all strokes and 1.63 (95% CI: 1.11–2.39) for ischemic strokes.

Conclusion: The results indicate that arsenic in drinking water even at low concentration is associated with higher incidence rate of stroke.

1. Introduction

Stroke is a leading cause of death and disability worldwide. Stroke ranks number four among all causes of death (Go et al., 2014), and globally stroke produces huge health burdens (Mozaffarian et al., 2015). Risk factors include age, sex, smoking, obesity and environmental factors such as air pollution and traffic noise (Andersen et al., 2012; Sørensen et al., 2011; Scheers et al., 2015).

Arsenic is a ubiquitous metalloid in the crust of the earth. Humans are exposed to arsenic through ingestion of water and food. The organic

Abbreviations: CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; IQR, interquartile range; DCH, the Diet, Cancer, and Health cohort; TWA, time-weighted average

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form of arsenic is most abundant in food, whereas in drinking water, arsenic is present in the inorganic form, which is associated with several chronic health consequences, thus representing a threat to human health. The World Health Organization guidelines recommend an upper limit of 10 μg/L arsenic in drinking water (WHO, 2010, 2011). The guideline value for arsenic in drinking water in Denmark was lowered in 2001 from 50 μg/L to 5 μg/L at the exit of waterworks and 10 μg/L at the consumers tap and further lowered to 5 μg/L at the consumers tap in 2017 (Ministry of Environment and Food of Denmark, 2016, 2017).

Epidemiological studies have indicated that ingestion of high concentrations of arsenic is associated with higher risks of various cancers (IARC, 2012). In addition, concentrations of arsenic > 100 μg/L in drinking water have consistently been associated with higher risk of cardiovascular disease (Cosselman et al., 2015). A meta-analysis from 2012 of 31 epidemiological studies of the effects of arsenic in drinking water on cardiovascular health concluded that there was an association between high arsenic concentrations above 50 μg/L and coronary heart disease, stroke, and peripheral arterial disease, whereas studies on lower arsenic concentrations were inconclusive (Moon et al., 2012). The pooled relative risk of stroke was 1.08 (95% CI: 0.98; 1.19) for high arsenic concentrations (> 50 μg/L) and 1.07 (95% CI: 0.96; 1.20) for low to moderate arsenic concentrations (Moon et al., 2012). A meta-analysis from 2017 estimated the pooled relative risk of stroke (ischemic, haemorrhage) comparing 20 μg/L with 10 μg/L water arsenic concentration at 1.08 (95% CI: 0.99; 1.17) for incident stroke and 1.06 (95% CI: 0.93; 1.20) for stroke mortality (Moon et al., 2017). Four cohort studies have supported an association between arsenic concentration below 50 μg/L arsenic in drinking water and cerebrovascular mortality including stroke and incident myocardial infarction (Chen et al., 2013; D'Ippoliti et al., 2015; Rahman et al., 2014; Monrad et al., 2017). One study found no overall association between toenail arsenic and stroke, but showed an increased risk of ischemic heart disease mortality among long-term smokers (Farzan et al., 2015). Two studies examined the association between urinary arsenic and stroke. Both studies showed an increased risk of stroke for methylated arsenic species (Tsinovio et al., 2018; Moon et al., 2013).

The underlying biological mechanisms linking inorganic arsenic with incidence rate of stroke are not clear, but are believed to include generation of reactive oxygen species (ROS) and oxidative stress, which can lead to or worsen endothelial dysfunction (Ellinsworth, 2015). Furthermore, studies have shown that inorganic arsenic influences inflammatory response and thereby endothelial dysfunction (Ellinsworth, 2015; Barchowsky et al., 1999), which may play a role in the pathogenesis of stroke (Cosentino et al., 2001).

The aim of the present study was to examine the association between arsenic in drinking water at low concentration and incidence rate of stroke in a prospective cohort with 16 years of follow-up.

2. Material and methods

2.1. Study population and design

The study was based on the Danish Diet, Cancer, and Health (DCH) prospective cohort (for details, see Tjønneland et al., 2007). A random sample of 160,725 residents in the two cities, Copenhagen and Aarhus without a diagnosis of cancer in the Danish Cancer Registry (Gjerstorff, 2011), were invited to participate in the study. A total of 57,053 individuals (age 50–64 years, born in Denmark) accepted the invitation and were enrolled in the cohort between 1993 and 1997. At enrolment, each individual completed a self-administered, interviewer-checked, lifestyle questionnaires covering smoking habits (status, intensity and duration), diet, beverages, physical activity and length of school attendance. Also, height, weight and waist circumference were measured by trained staff members using standardized protocols, from which BMI was calculated.

The DCH cohort was established in accordance with the Helsinki Declaration and approved by the local Ethics Committees. Written informed consent was obtained from all study individuals.

2.2. Strokes

Incident stroke (i.e. first ever) was identified by linkage of the cohort with the Danish National Patient Register with nationwide data on all non-psychiatric hospital admissions since 1977 (Lynge et al., 2011). Since 1995, patients discharged from emergency departments and outpatient clinics have also been registered. Stroke was defined based on International Classification of Disease (ICD) ICD-8 codes: 430, 431, 433, 434, 436.01, or 436.90 until 1994 and ICD-10 codes: I60, I61, I63 or I64 from 1994. Both primary and secondary discharge stroke diagnoses were used. Stroke diagnoses between baseline and end of follow-up (30 November 2009) were validated by review of medical records by a physician with neurological experience (Lühdorf et al., 2017). The overall positive predictive value for a stroke diagnosis was 69.3% (95% CI: 67.8; 70.9), highest in inpatient clinics in neurology, medical stroke unit and neurosurgery (83.5%–87.8%) and lowest in outpatient clinics (43%). Stroke was defined as rapid onset of focal or global neurological deficit of vascular origin that persisted beyond 24 h, leading to either death or confirmed by CT or MRI scan showing a lesion suggestive of a stroke. Based on CT, MRI, autopsy records and lumbar punctures, we subsequently categorized strokes in following sub-diagnoses: haemorrhage strokes, ischemic stroke and other. Only diagnoses confirmed in the validation study were included in the present study.

2.3. Exposure assessment

Residential addresses (present and past) and dates of movements (to and from each address) for all individuals between 1973 and date of stroke diagnosis or end of follow-up were extracted from the Danish Civil Registration System (Pedersen, 2011). Residential addresses have a unique identification code based on municipality, road, and house. Addresses were geocoded by merging the addresses with a database with official addresses in Denmark.

The method used to obtain the arsenic concentrations in Danish drinking water for the study population has been described in details elsewhere (Baastrup et al., 2008). In brief, arsenic concentrations in the outlet water of water utilities were obtained from the Jupiter database, which is managed by the Geological Survey of Denmark and Greenland (Thomsen et al., 2004). According to Danish legislation, arsenic concentration in drinking water should be monitored and reported to the Jupiter database since 2001 (Ministry of Environment and Food of Denmark, 2015). The geographical location (coordinates) of the water utilities was obtained from the Jupiter database. Arsenic concentration in drinking water have been analysed by different certified laboratories in Denmark. ICP-MS (inductively coupled plasma mass spectrometry) is the frequently used method with a detection limit of 0.03 μg/L.

Mean arsenic concentration was calculated for each utility using 4954 measurements from the outlet water pipe distributing tap water to households in 2487 water utilities in the period 1987–2004. Most of the measurements used for the exposure assessment were collected in the period 2002–2004 with 100% data coverage of the arsenic concentrations in the Danish public waterworks since 2002. The mean arsenic concentration for each utility was used as a measure of arsenic concentrations throughout the study period 1973–2009 (Baastrup et al., 2008). The 2487 water utilities were connected to 94 water supply areas. A water volume-weighted average arsenic concentration was calculated for each water supply area (Baastrup et al., 2008).

Arsenic concentration at residential addresses was obtained by linkage of addresses with water supply areas. Hereby, arsenic concentration was available at 98% of the addresses.

Exposure to arsenic in drinking water was derived as a time-varying exposure calculated as the time-weighted average (TWA) concentration of arsenic at any time in the study period 1993–2009 for each

individual. The 20-year TWA arsenic concentration was used as the primary exposure variable based on addresses during a preceding 20-year period. The 20-year TWA arsenic concentration was categorized in quartiles among all individuals. We had no a priori reason for selecting a 20-year exposure window. However, by choosing a 20-year exposure window, we took full advantage of the unique possibility to retrieve address history of the participants. As a secondary exposure variable, highest ever arsenic concentration was analysed. It was defined for each individual as ever been exposed to at least 2, 5 or 10 μg/L arsenic concentration in the drinking water, respectively. Highest ever arsenic concentration was a time-varying variable with the value 0 until date of exposure to highest arsenic (at least 2, 5 or 10 μg/L, respectively) at which date the value changed to 1.

2.4. Covariates

We adjusted the models for the potential confounders as defined a priori, and available from the questionnaire completed at enrolment by each individual: age (5-year intervals), sex, calendar year (5-year intervals), body mass index (BMI; kilograms per meter squared), waist circumference (centimetres), smoking status (never, former, current), smoking duration (years), smoking intensity (gram tobacco/day), alcohol consumption (yes, no), intake of alcohol (gram/day), intake of vegetables (g/day), intake of fruit (g/day), physical activity (metabolic equivalent (MET) score) and length of school attendance (7 years or less, 8–10 years, > 10 years).

2.5. Statistical methods

We employed a generalized linear model to evaluate the associations between exposure to arsenic in drinking water and incidence rate of stroke. The outcome variable of the analyses was stroke (all strokes and stratified by subtypes of stroke: ischemic stroke and haemorrhage stroke). The association between 20-year TWA arsenic concentration and the incidence rate of stroke was the primary analysis. Furthermore, we evaluated the association between highest ever arsenic concentration at an address and the incidence rate of stroke for 2, 5 and 10 μg/L arsenic in the drinking water, respectively. We analysed all cohort data combined and stratified by city of enrolment (Copenhagen and Aarhus), because the concentration of arsenic in drinking water differed between the two areas (Fig. 1).

In the generalized linear model, we used a Poisson distribution of number of stroke cases and logarithmic transformation of risk time as offset value, also known as piece-wise exponential model (Laird and Oliver, 1981). Follow-up time started at date of enrolment (1993–1997) for all individuals. Risk-time for each individual was calculated as time from enrolment until diagnosis of stroke, death, emigration or end of the study (November 2009), whichever came first. It is assumed that the incidence rate of stroke is constant within each time interval in the analysis. Therefore, risk time was split by age (5-year age groups) and calendar year (5-year intervals) using the SAS Lexis macro (Carstensen, 2007), resulting in approximately constant incidence rates of stroke. As opposed to a standard Cox regression analysis, more than one time scale can be examined by using the generalized linear model with a Poisson distribution of incidence rates. In the present analysis, the following three time scales were included: age, calendar year and time since inclusion in the study.

Incidence rate ratios (IRR) for stroke (all strokes and stratified by subtype of stroke) were estimated for exposure to arsenic in a semi-adjusted model (i.e. adjusted for age in 5-year intervals, sex and calendar year in 5-year intervals), and in a fully adjusted model further including body mass index, waist circumference, smoking (status, duration, and intensity), alcohol (consumption and intake), intake of fruit and vegetables, physical activity, and length of school attendance, as fixed effects. All results are presented as IRR with 95% confidence intervals (CI). We estimated IRR of stroke using the lowest concentration category as reference.

We examined if the association between 20-year TWA arsenic concentration and the incidence rate of stroke could be modelled with 20-year TWA arsenic concentration as a continuous exposure variable. A likelihood ratio test was used to compare a linear and categorical version of the exposure. We found that the association deviated from linearity. The assumption is that there is linearity between the continuous exposure variable and the logarithm of the incidence rate (log(incidence rate)). The deviation from linearity was illustrated by estimating the log(incidence rate) of stroke with 20-year TWA arsenic concentration categorized into 10 categories (deciles) overall and stratified by city of enrolment. For the main analysis, he 20-year TWA arsenic concentration was categories into quartiles among all individuals.

Five sensitivity analysed were performed. To examine the effect of the highest 20-year TWA arsenic concentrations, the first sensitivity analysis evaluated three categories of concentration of 20-year TWA arsenic with categories defined as lowest 50%, medium 40% and highest 10% arsenic concentrations. In the second sensitivity analysis, exposure to arsenic was evaluated by 5-year TWA arsenic concentration. As a third sensitivity analysis, effect modification by sex, age, smoking status, diabetes, hypertension and hypercholesterolemia was evaluated by including the interaction between 20-year TWA of arsenic concentration and sex (men versus women), age group (< median age versus ≥median age), smoking status (never versus ever), baseline diabetes (no versus yes), baseline hypertension (no versus yes) and baseline hypercholesterolemia (no versus yes) in the model, separately. Each interaction term was evaluated in a model adjusted for all baseline confounders and including both main effects of the interaction. A fourth sensitivity analysis repeated the main analysis among never smokers overall and stratified by city of enrolment. In the fifth sensitivity analysis, the main analysis stratified by city of enrolment was examined with the 20-year TWA arsenic concentration categorized using the same categories as for the total cohort.

All analyses were performed using the PROC GENMOD procedure of SAS version 9.4 (SAS Institute Inc.; Cary, NC).

3. Results

Among the 57,053 individuals enrolled in the cohort study, 574 were excluded due to cancer before enrolment (information in the registers was updated after enrolment) (Fig. 2). Individuals with a stroke diagnosis before enrolment were excluded (N = 572 individuals). Furthermore, 162 individuals were excluded because the medical record could not be located for validation of the diagnosis. A complete residential address history between 1973 and event or censoring date was missing for 1169 individuals. A total of 635 individuals were excluded due to missing data on one or more covariates leaving a study population of 53,941 individuals.

Among the 53,941 individuals, a total of 2195 (4.1%) were admitted to hospital for incident stroke (n = 1801 ischemic stroke, and n = 381 haemorrhage stroke) between baseline and censoring. A total of 13 patients with a stroke diagnosis were categorized as other strokes as these patients were discharged without a brain scan and could therefore not be classified as ischemic or haemorrhage stroke. In total, 180 (8.2%) incident strokes were fatal (n = 60 (3.3%) ischemic strokes were fatal; n = 116 (30.5%) haemorrhage strokes were fatal; and n = 4 (30.8%) other strokes were fatal). The mean follow-up was 12.8 years, providing an incidence rate of stroke at 315 per 100,000 person years at risk (Copenhagen: 261, Aarhus: 321). The incidence rate for the subtypes of stroke was 259 and 55 per 100,000 person years at risk for ischemic and haemorrhage stroke, respectively.

At enrolment, the median arsenic concentration in drinking water at residential addresses was 0.7 μg/L (range: 0.03–25.3 μg/L) (Fig. 1). The median concentration was 3.5 times higher among individuals enrolled in Aarhus as compared to individuals enrolled in Copenhagen (2.1

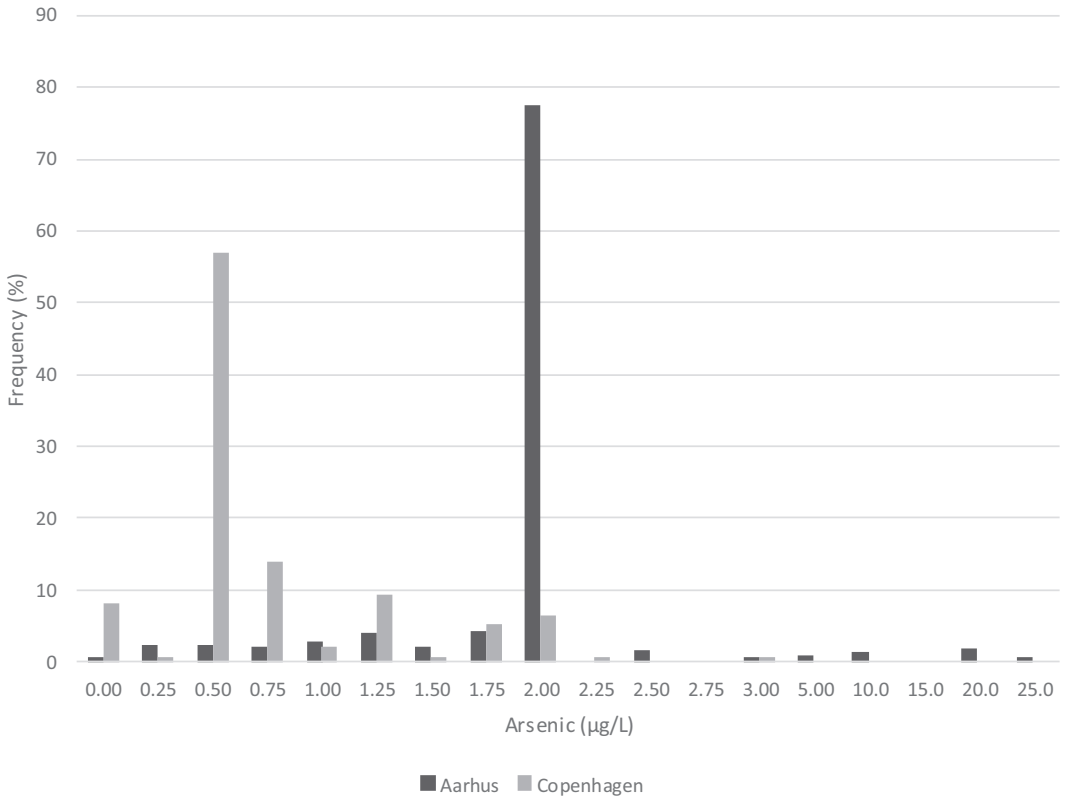

Fig. 1. Frequency distribution of baseline arsenic concentration at the city of residence at enrolment of 53,941 individuals.

versus 0.6 µg/L).

Baseline characteristics according to quartile arsenic concentration at residential addresses at enrolment are shown in Table 1. Individuals in the second quartile (i.e. exposed to 0.57–0.70 µg/L As at baseline) were more likely to have a short school attendance, being current smokers, have a low intake of fruit and vegetables and have diabetes. Individuals in the fourth quartile (i.e. exposed to 1.93–25.3 µg/L As at baseline) were more likely have a short school attendance and have a low intake of fruit and vegetables. The majority of individuals with arsenic concentration at the enrolment addresses in the three lowest quartiles lived in Copenhagen at enrolment.

We found an association between 20-year TWA arsenic concentration and incidence rate of stroke, with an adjusted IRR of 1.17 (95% CI: 1.04–1.32) when comparing the highest quartile (1.93–25.34 µg/L) with the lowest quartile (0.049–0.57 µg/L) (Table 2). The association did not follow a monotonic exposure-response relationship, since the IRR was highest for the second quartile. We found no association in the Copenhagen area, where incidence rates were almost identical in the lowest and highest quartile, whereas in the Aarhus area the highest quartile (2.11–25.34 µg/L) was associated with an IRR of 1.79 (95% CI: 1.41–2.26) when compared with the lowest quartile (0.085–1.83 µg/L). Deviation from linearity between 20-year TWA arsenic concentration and log(incidence rate) of stroke is illustration in Supplementary Fig. I. Online Table I shows similar results for 5-year TWA arsenic concentration and stroke.

The IRR for ischemic stroke for the total cohort was highest for the second quartile with an IRR of 1.31 (95% CI: 1.15–1.49). In the Copenhagen area, the IRR was 1.18 (95% CI: 1.01–1.38) for the second

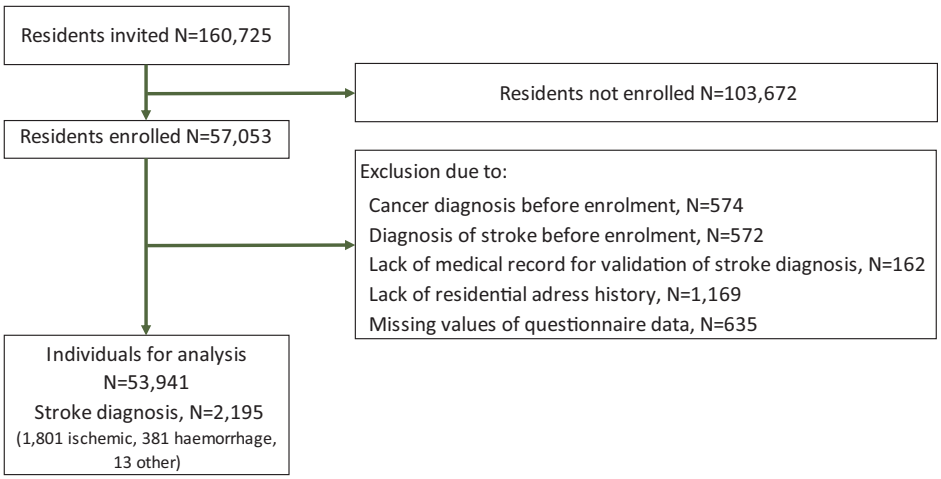

Fig. 2. Flow diagram of data in the Danish prospective cohort Diet, Cancer, and Health.

Table 1
Baseline characteristics by quartile arsenic concentration at the residence at enrolment of 53,941 individuals.

Characteristic at enrolment	N	As (μg/L)			
		Q_1 (0.030–0.572)	Q_2 (0.573–0.700)	Q_3 (0.701–2.000)	Q_4 (2.001–25.34)
All individuals, n (%)	53,941	12,040 (22.3)	13,022 (24.1)	16,042 (29.7)	12,837 (23.8)
Age at enrolment, years mean (SD)		56.8 ± 4.3	56.7 ± 4.4	56.6 ± 4.3	56.4 ± 4.4
Sex, n (%)					
Male	25,497	5698 (47.3)	6042 (46.4)	7553 (47.1)	6204 (48.3)
Female	28,444	6342 (52.7)	6980 (53.6)	8489 (52.9)	6633 (51.7)
Length of school attendance, n (%)					
≤7 years	17,790	3520 (29.2)	5061 (38.9)	4348 (27.1)	4861 (37.9)
8–10 years	24,930	5889 (48.9)	5761 (44.2)	7659 (47.7)	5621 (43.8)
≥10 years	11,221	2631 (21.9)	2200 (16.9)	4035 (25.2)	2355 (18.3)
Smoking status, n (%)					
Never	19,224	4688 (39.0)	3932 (30.2)	5994 (37.4)	4610 (35.9)
Former	15,140	3460 (28.7)	3366 (25.8)	4676 (29.2)	3638 (28.3)
Current	19,577	3892 (32.3)	5724 (44.0)	5372 (33.5)	4589 (35.8)
Smoking duration[a], years median (IQR)		32 (1–38)	34 (1–39)	31 (1–38)	32 (1–38)
Intensity[a], g/day median (IQR)		3 (0–16)	10 (0 – 20)	4 (0–15)	6 (0–18)
Alcohol consumption, n (%)		11,779 (97.8)	12,623 (96.9)	15,755 (98.2)	12,537 (97.7)
Alcohol intake[b], g/day mean (SD)		21.3 ± 21.0	22.3 ± 25.3	21.7 ± 20.9	18.2 ± 19.2
Fruit intake, g/day mean (SD)		213.5 ± 158.5	209.0 ± 180.2	214.4 ± 160.6	207.0 ± 158.4
Vegetable intake, g/day mean (SD)		182.1 ± 103.4	175.2 ± 114.2	184.3 ± 100.4	172.7 ± 96.6
BMI, kg/m^2 mean (SD)		26.0 ± 3.9	26.3 ± 4.3	25.9 ± 3.9	26.0 ± 4.0
Waist circumference, cm mean (SD)		88.3 ± 12.4	88.7 ± 13.0	88.5 ± 12.5	89.0 ± 12.7
Physical activity, MET score mean (SD)		66.8 ± 41.8	73.3 ± 52.6	65.0 ± 40.5	62.2 ± 40.8
Diabetes, n (%)		228 (1.9)	338 (2.6)	301 (1.9)	214 (1.7)
Hypertension, n (%)		6090 (50.6)	6566 (51.0)	8006 (50.0)	5919 (46.2)
Hypercholesterolemia, n (%)		5559 (46.2)	5956 (45.7)	6811 (42.5)	5616 (43.8)
City at enrolment, n (%)					
Copenhagen	37,549	11,448 (95.1)	12,860 (98.8)	12,238 (82.5)	3 (0.1)
Aarhus	16,392	592 (4.9)	162 (1.2)	2804 (17.5)	12,834 (99.9)

As: arsenic concentration in drinking water; SD: standard deviation; IQR: interquartile range.
[a] Among present and former smokers (N = 34,717).
[b] Among individuals with alcohol consumption (N = 52,694).

Table 2
Association between quartile (Q) of 20-year time weighted average (TWA) arsenic concentration in drinking water and incidence rate of all strokes.

20-year TWA arsenic (μg/L)		Cases (n)	Person years	IR per 100,000 person years	IRR (95% CI)	
Range	Median				Crude[a]	Adjusted[b]
Total cohort						
Q_1: 0.049–0.573	0.435	486	172,202	282.2	1.00 (ref.)	1.00 (ref.)
Q_2: 0.573–0.760	0.584	657	180,891	363.2	1.32 (1.17–1.48)	1.21 (1.07–1.36)
Q_3: 0.760–1.933	1.174	475	169,470	280.3	1.05 (0.92–1.19)	1.05 (0.92–1.19)
Q_4: 1.933–25.34	2.109	577	173,856	331.9	1.22 (1.08–1.37)	1.17 (1.04–1.32)
Copenhagen						
Q_1: 0.049–0.489	0.425	349	121,240	287.9	1.00 (ref.)	1.00 (ref.)
Q_2: 0.489–0.573	0.573	458	129,707	353.1	1.21 (1.05–1.39)	1.09 (0.95–1.26)
Q_3: 0.573–0.870	0.679	379	116,706	324.7	1.14 (0.99–1.32)	1.08 (0.93–1.25)
Q_4: 0.870–16.62	1.250	331	117,890	280.7	1.01 (0.87–1.17)	1.02 (0.88–1.18)
Aarhus						
Q_1: 0.085–1.834	1.306	145	52,006	278.8	1.00 (ref.)	1.00 (ref.)
Q_2: 1.834–2.109	2.067	117	41,796	279.9	0.83 (0.64–1.06)	0.81 (0.62–1.04)
Q_3: 2.109–2.109	2.109	253	72,414	349.4	1.11 (0.90–1.37)	1.09 (0.88–1.34)
Q_4: 2.109–25.34	2.109	163	44,650	365.1	1.83 (1.44–2.31)	1.79 (1.41–2.26)
Total cohort, sensitivity analysis						
50% lowest: 0.049–0.760	0.573	1143	353,093	323.7	1.00 (ref.)	1.00 (ref.)
40% medium: 0.760–2.109	1.693	819	279,534	293.0	0.89 (0.82–0.98)	0.91 (0.83–1.00)
10% highest: 2.109–25.34	2.109	233	63,792	365.2	1.50 (1.29–1.73)	1.49 (1.28–1.72)

IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; Q_1–Q_4, quartiles 1–4.
[a] Adjusted for age, sex and calendar year.
[b] Adjusted for age, sex, body mass index, waist circumference, smoking status, smoking duration, smoking intensity, alcohol status, intake of alcohol, physical activity, fruit intake, vegetable intake, length of school attendance, and calendar year.

quartile and 1.19 (95% CI: 1.01–1.39) for the third quartile. In the Aarhus area the IRR was 1.83 (95% CI: 1.41–2.37) for the highest quartile. Overall, the pattern was similar for ischemic and haemorrhage stroke, both not following a monotonic exposure-response relationship and showing higher incidence rate in association with the upper concentration quartile for the total cohort, which was driven by the Aarhus area; for haemorrhage stroke, with fewest cases, none of these results were statistical significant (Tables 3 and 4).

Table 3
Association between quartile (Q) of 20-year time weighted average (TWA) arsenic concentration in drinking water and incidence rate of ischemic strokes.

20-year TWA arsenic (μg/L)		Cases (n)	Person years	IR per 100,000 person years	IRR (95% CI)	
Range	Median				Crude[a]	Adjusted[b]
Total cohort						
Q_1: 0.049–0.573	0.435	390	172,202	226.5	1.00 (ref.)	1.00 (ref.)
Q_2: 0.573–0.760	0.584	566	180,891	312.9	1.42 (1.25–1.61)	1.31 (1.15–1.49)
Q_3: 0.760–1.933	1.174	386	169,470	227.8	1.06 (0.92–1.22)	1.06 (0.92–1.23)
Q_4: 1.933–25.34	2.109	459	173,856	264.0	1.21 (1.05–1.38)	1.16 (1.01–1.33)
Copenhagen						
Q_1: 0.049–0.489	0.425	275	121,240	226.8	1.00 (ref.)	1.00 (ref.)
Q_2: 0.489–0.573	0.573	387	129,707	298.4	1.30 (1.11–1.52)	1.18 (1.01–1.38)
Q_3: 0.573–0.870	0.679	329	116,706	281.9	1.26 (1.07–1.48)	1.19 (1.01–1.39)
Q_4: 0.870–16.62	1.250	275	117,890	233.2	1.06 (0.90–1.26)	1.08 (0.91–1.27)
Aarhus						
Q_1: 0.085–1.834	1.306	118	52,006	226.9	1.00 (ref.)	1.00 (ref.)
Q_2: 1.834–2.109	2.067	89	41,796	212.9	0.75 (0.56–1.00)	0.73 (0.55–0.97)
Q_3: 2.109–2.109	2.109	193	72,414	266.5	1.06 (0.83–1.34)	1.03 (0.81–1.30)
Q_4: 2.109–25.34	2.109	135	44,650	302.3	1.90 (1.46–2.46)	1.83 (1.41–2.37)
Total cohort, sensitivity analysis						
50% lowest: 0.049–0.760	0.573	956	353,093	270.8	1.00 (ref.)	1.00 (ref.)
40% medium: 0.760–2.109	1.693	653	279,534	233.6	0.85 (0.77–0.94)	0.88 (0.79–0.97)
10% highest: 2.109–25.34	2.109	192	63,792	301.0	1.50 (1.28–1.76)	1.49 (1.27–1.75)

IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; Q_1–Q_4, quartiles 1–4.
[a] Adjusted for age, sex and calendar year.
[b] Adjusted for age, sex, body mass index, waist circumference, smoking status, smoking duration, smoking intensity, alcohol status, intake of alcohol, physical activity, fruit intake, vegetable intake, length of school attendance, and calendar year.

Table 4
Association between quartile (Q) of 20-year time weighted average (TWA) arsenic concentration in drinking water and incidence rate of haemorrhage strokes.

20-year TWA arsenic (μg/L)		Cases (n)	Person years	IR per 100,000 person years	IRR (95% CI)	
Range	Median				Crude[a]	Adjusted[b]
Total cohort						
Q_1: 0.049–0.573	0.435	92	172,202	53.4	1.00 (ref.)	1.00 (ref.)
Q_2: 0.573–0.760	0.584	86	180,891	47.5	0.90 (0.67–1.21)	0.84 (0.63–1.14)
Q_3: 0.760–1.933	1.174	87	169,470	51.3	1.00 (0.75–1.35)	0.99 (0.74–1.33)
Q_4: 1.933–25.34	2.109	116	173,856	66.7	1.28 (0.98–1.69)	1.23 (0.94–1.63)
Copenhagen						
Q_1: 0.049–0.489	0.425	71	121,140	58.6	1.00 (ref.)	1.00 (ref.)
Q_2: 0.489–0.573	0.573	69	129,707	53.2	0.90 (0.64–1.25)	0.85 (0.61–1.19)
Q_3: 0.573–0.870	0.679	45	116,760	38.6	0.67 (0.46–0.98)	0.64 (0.44–0.94)
Q_4: 0.870–16.62	1.250	55	117,900	46.6	0.81 (0.57–1.16)	0.81 (0.57–1.16)
Aarhus						
Q_1: 0.085–1.834	1.306	27	52,006	51.9	1.00 (ref.)	1.00 (ref.)
Q_2: 1.834–2.109	2.067	27	41,796	64.6	1.18 (0.68–2.04)	1.12 (0.65–1.96)
Q_3: 2.109–2.109	2.109	60	72,414	82.9	1.36 (0.85–2.16)	1.32 (0.83–2.11)
Q_4: 2.109–25.34	2.109	27	44,650	60.5	1.49 (0.85–2.61)	1.44 (0.82–2.52)
Total cohort, sensitivity analysis						
50% lowest: 0.049–0.760	0.573	178	353,093	50.4	1.00 (ref.)	1.00 (ref.)
40% medium: 0.760–2.109	1.693	163	279,534	58.3	1.13 (0.92–1.41)	1.14 (0.92–1.42)
10% highest: 2.109–25.34	2.109	40	63,792	62.7	1.56 (1.10–2.22)	1.54 (1.08–2.20)

IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; Q_1–Q_4, quartiles 1–4.
[a] Adjusted for age, sex and calendar year.
[b] Adjusted for age, sex, body mass index, waist circumference, smoking status, smoking duration, smoking intensity, alcohol status, intake of alcohol, physical activity, fruit intake, vegetable intake, length of school attendance, and calendar year.

Having ever lived at an address with 10 μg/L or more arsenic in the drinking water was associated with an IRR of 1.44 (95% CI: 1.00–2.08) for all strokes and an IRR of 1.63 (95% CI: 1.11–2.39) for ischemic strokes (Table 5).

Changing categorization of the 20-year TWA arsenic concentration from quartiles to three categories for the total cohort in the first sensitivity analysis showed that exposure to the 10% highest arsenic concentration compared to the 50% lowest arsenic concentrations resulted in IRR of 1.49 (95% CI: 1.27–1.75) for total strokes, and 1.49 (95% CI: 1.28–1.72) for ischemic strokes, and 1.54 (1.08–2,20) for haemorrhage

Table 5
Association between highest ever arsenic concentration at an address and incidence rate of strokes overall and stratified by type of stroke.

Highest ever arsenic concentration (μg/L)	Cases, persons (n)[c]	Person years	IR per 100,000 person years	IRR (95% CI)	
				Crude[a]	Adjusted[b]
Stroke					
≥2 vs < 2	762, 19,043	244,857	311.2	1.01 (0.93–1.11)	1.02 (0.93–1.11)
≥5 vs < 5	68, 1513	19,628.3	346.4	1.15 (0.91–1.47)	1.12 (0.88–1.43)
≥10 vs < 10	29, 484	6452.7	449.4	1.42 (0.99–2.05)	1.44 (1.00–2.08)
Ischemic stroke					
≥2 vs < 2	603, 19,043	244,857	246.3	0.96 (0.87–1.06)	0.96 (0.87–1.06)
≥5 vs < 5	60, 1513	19,629	305.7	1.24 (0.96–1.61)	1.20 (0.93–1.56)
≥10 vs < 10	27, 484	6453	481.4	1.61 (1.10–2.36)	1.63 (1.11–2.39)
Haemorrhage strokes					
≥2 vs < 2	156, 19,043	244,857	63.7	1.32 (1.07–1.62)	1.33 (1.08–1.64)
≥5 vs < 5	8, 1513	19,629	40.8	0.78 (0.39–1.56)	0.77 (0.38–1.55)
≥10 vs < 10	2, 484	6453	31.0	0.57 (0.14–2.30)	0.59 (0.15–2.37)

IRR, incidence rate ratio; CI, confidence interval.
[a] Adjusted for age, sex and calendar year.
[b] Adjusted for age, sex, body mass index, waist circumference, smoking status, smoking duration, smoking intensity, alcohol status, intake of alcohol, physical activity, fruit intake, vegetable intake, length of school attendance, and calendar year.
[c] Number of cases and persons, respectively, in the group with exposure above the cut-off points.

strokes (Tables 2, 3 and 4). Exposure to 5-year TWA arsenic concentration showed more pronounced IRRs for the fourth quartile compared to the first quartile for total strokes (IRR = 2.10, 95% CI: 1.63–2.71) and ischemic strokes (IRR = 2.24, 95% CI: 1.70–2.95) in Aarhus area (Supplementary Tables I, II and III). There were no statistically significant effect modifications of the association between 20-year TWA arsenic concentration in drinking water and stroke by sex, age, smoking status, diabetes, hypertension and hypercholesterolemia (Supplementary Table IV). The main analysis of the association between 20-year TWA arsenic concentration and incidence rate of stroke (overall, and stratified by city of enrolment) was repeated among never smokers. It showed an attenuated effect except for individuals enrolled in the Aarhus area (Supplementary Table V). In the main analysis stratified by city of enrolment, the 20-year TWA arsenic concentration categories were derived for each city. The fifth sensitivity analysis repeated the analysis using the total cohort exposure categories for each city of enrolment (Supplementary Table VI).

4. Discussion

We found a higher incidence rate of stroke associated with higher concentration of arsenic in drinking water. This was seen in the total cohort, but was more pronounced among individuals enrolled in the Aarhus area with highest arsenic concentrations. Individuals ever exposed to arsenic concentrations above the guideline value (5 μg/L) had no increased incidence rate of stroke. However, individuals ever exposed to ≥10 μg/L had an increased incidence rate of stroke, especially for ischemic stroke.

The strengths of our study include the prospective design with information on various potential lifestyle and socioeconomic confounders collected at enrolment limiting the risk of recall bias, the large number of individuals with stroke, inclusion of incident strokes and access to residential address history. Furthermore, individuals with stroke were identified using the nationwide Danish National Patient Register of high quality, and validated by reviewing medical records. Finally, we had a high degree of linkage between residential addresses and water supply area with measurements of arsenic concentrations in the drinking water.

The present study has also some limitations in exposure assessment and in potential confounding. First, the arsenic concentration was based on measurements at the water utilities outlets and not on drinking water tapped in the homes. Under certain conditions there might be precipitation of arsenic in the distribution pipes or dissolving of arsenic from the pipes into the water (EPA USEPA, 2007). However, a study showed low arsenic release to drinking water in Denmark (Nielsen et al., 2006). A second limitation is that arsenic concentrations used to estimate the time-weighted average of arsenic concentrations in the period 1973–2009 were based on measurements in the period 1987–2004. However, in a previous study, we showed only a weak tendency towards changes in drilling depth over an 18-year period based on 3396 observations (Baastrup et al., 2008). Drilling depth explained only 4% of the variation in arsenic concentration. A third limitation is the lack of information on individual-level tap water consumption and the lack of validation of the estimated arsenic exposure.

A fourth limitation is the lack of information about the intake of arsenic from other sources than drinking water. Tap water is the major source of drinking water in Denmark, and consumption of bottled water in Denmark is among the lowest in the EU (20 L per person per year) (Rygaard et al., 2009). Arsenic in food is usually the less harmful organic form. Altogether, the tap water arsenic concentrations in the present study is associated with some uncertainty. Finally, a fifth limitation is that information on diet and lifestyle factors may be imprecise partly because of imprecise reporting of e.g. diet at baseline, and partly because of changes in diet and lifestyle during follow-up. On the other hand, diet and lifestyle habits are often relatively stable in the elderly age group considered here. We would also expect this misclassification to be unrelated to the disease and arsenic concentration. However, we cannot rule out that residual confounding or chance has influenced our results. The non-monotonic exposure-response association, with the highest IRR in the second (vs. first) quartile and the next highest IRR in the fourth quartile, follows the pattern of lower socioeconomic status and lower intake of fruits and vegetables in these quartiles, as well as the higher prevalence of current smoking and diabetes in the second quartile. However, adjustment for educational level, fruit and vegetable intake, smoking and other co-variates did not affect the risk estimate in highest arsenic exposure group much, which is contraindicative of substantial residual confounding from the factors adjusted for. We cannot exclude confounding from unknown or unaccounted for risk factors. Further, there was not much difference between the arsenic-stroke association among diabetics and non-diabetics (Supplementary Table IV).

The study population was enrolled in two cities. Copenhagen is the capital of Denmark and has a larger population than Aarhus. Similar levels of air pollution (NO_2, $PM_{2.5}$) measured at background stations over the last two decades are seen in Copenhagen and Aarhus, whereas

street concentrations were a little higher in Copenhagen than in Aarhus, probably due to more car traffic in Copenhagen. Copenhagen and Aarhus have followed the same pattern of industrialization, and since the 1970es de-industrialization. For several decades both areas have been dominated by administration, service industry and educational institutions. There is not much heavy industry in any of the cities but both cities have a busy harbor. In Aarhus, drinking water mainly comes from sandy quaternary aquifers, while in Copenhagen drinking water abstraction is mainly from chalk aquifers. This affect the chemical composition of the groundwater, including a higher degree of hardness of the drinking water in Copenhagen.

High arsenic concentration (> 50 μg/L) in drinking water has been associated with higher incidence rate of stroke, but less is known about associations between low-level exposure to arsenic and incidence rate of stroke (Moon et al., 2012). A recent cohort study of arsenic in drinking water and stroke mortality in Bangladesh including 1033 cases among 61,074 individuals found a higher risk of stroke mortality with drinking water arsenic concentrations between 10 and 49 μg/L compared with below 10 μg/L (hazard ratio, HR = 1.20 (95%CI: 0.92–1.57), higher for females, HR = 1.31 (95%CI: 0.87–1.98) than males, HR = 1.12, (95%CI: 0.78–1.60)) (Rahman et al., 2014). Likewise, an Italian cohort study suggested that arsenic exposure from drinking water of 10–20 μg/L and above 20 μg/L were associated with higher mortality from stroke when compared to below 10 μg/L (hazard ratio, HR for 10–20 μg/L as compared to < 10 μg/L, HR = 1.47 (95%CI: 1.14–1.90) for males and HR = 1.23 (0.99–1.52) for females) (D'Ippoliti et al., 2015). These previous studies provide some evidence for a relationship between low-level exposure to arsenic in drinking water and stroke, but they have not investigated the relationship at concentrations as low as in the present study. Also, these previous studies have focused on stroke mortality instead of stroke incidence as in the present study. We found an association between incident stroke (both for all strokes and ischemic stokes) and drinking water arsenic concentration between 1.93 and 25.3 μg/L in the total cohort and between 2.11 and 25.3 μg/L in the Aarhus area when compared to below 0.57 and 1.8 μg/L, respectively. We found no association in the Copenhagen enrolment area with generally lower arsenic concentrations. Having ever been exposed to 10 μg/L or more arsenic concentration was associated with a higher incidence of stroke (IRR = 1.44 (95%CI: 1.00–2.08) for all strokes) for the total cohort. This estimate is of similar size as seen in the study Italian study by D'Ippoliti et al. (D'Ippoliti et al., 2015). However, estimates obtained by Rahman et al. were lower (Rahman et al., 2014). Finally, the pooled relative risk of incident stroke obtained in the meta-analysis by Moon et al. was even lower (Moon et al., 2017). This calls for a cautious interpretation of our results.

This is the first study to report an association between exposure to arsenic in drinking water at such low concentrations and incidence rate of stroke. Therefore, further studies are needed to confirm the findings in the present study.

5. Conclusion

Our study indicated that low-level exposure to arsenic in drinking water (< 50 μg/L) is associated with an increased incidence rate of stroke. The association is stronger for ischemic stroke compared to haemorrhage stroke. Further research is needed to elucidate the underlying mechanisms behind these findings.

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Conflicts

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

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