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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