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Natural fluoride in drinking water and myocardial infarction: A cohort study in Sweden

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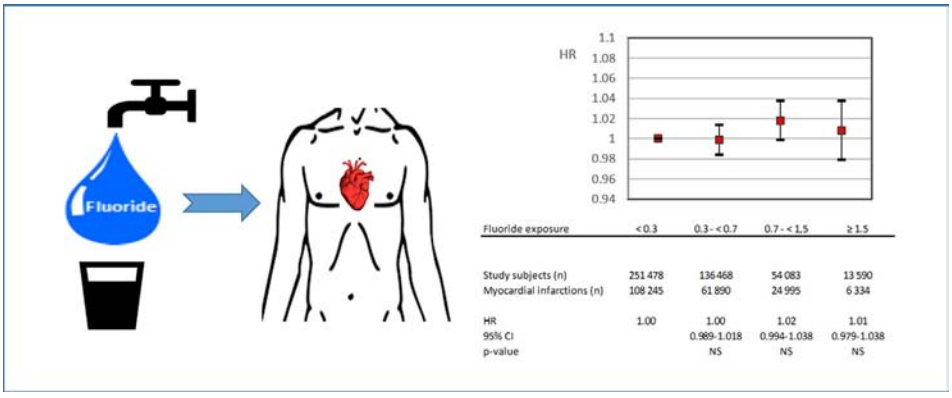
HIGHLIGHTS

- We conducted a nationwide cohort study on fluoride exposure and MI.
- Association between drinking water fluoride and MI was investigated.
- Trace elements in the drinking water are implicated in the pathogenesis of CHD.
- Natural fluoridated drinking water at concentrations 0.1–2.7 mg/l was assessed.
- No increase in the overall risk of MI related to fluoride in drinking water.

GRAPHICAL ABSTRACT



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ABSTRACT

Large geographical variation in the coronary heart disease (CHD) incidence is seen worldwide and only a part of this difference is attributed to the classic risk factors. Several environmental factors, such as trace elements in the drinking water have been implicated in the pathogenesis of CHD. The objective was to assess the association between drinking water fluoride exposure and myocardial infarction in Sweden using nationwide registers. This large cohort consisted of 455,619 individuals, born in Sweden between January 1, 1900 and December 31, 1919, alive and living in their municipality of birth at the time of start of follow-up. Estimated individual drinking water fluoride exposure was stratified into four categories: very low (<0.3 mg/l), low (0.3–<0.7 mg/l), medium (0.7–<1.5 mg/l) and high (≥1.5 mg/l). In Cox regression analyses, compared to the very low fluoride group, the adjusted Hazard Ratio for the low fluoride group was 0.99 (95% confidence interval, 0.98–1.00), for the medium fluoride group 1.01 (95% confidence interval, 0.99–1.03) and 0.98 (95% confidence interval, 0.96–1.01) for the highest fluoride group. Adding water hardness to the model did not change the results. We conclude that the investigated levels of natural drinking water fluoride content does not appear to be associated with myocardial infarction, nor related to the geographic myocardial infarction risk variation in Sweden. Potential misclassification of exposure and unmeasured confounding may have influenced the results.

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1. Introduction

A large geographical variation in the coronary heart disease (CHD) incidence is seen worldwide, as well as large regional differences within countries (Tunstall-Pedoe et al., 1994; WHO, 2008). In Sweden, a 30–40% increased incidence of myocardial infarction has been reported in the northern part of the country than in the south, and up to 60% respectively 53% higher mortality rate for ischemic heart disease for men and women, in the mid-west compared to the mid-east (Hammar et al., 1992; Nerbrand et al., 1991b). Only a part of the geographical variation seen in Sweden is explained by variations in classic CHD risk factors, such as advancing age, heredity, gender, race, high blood pressure, blood lipids, smoking, physical inactivity, diabetes, nutrition, obesity, hormone replacement therapy, low socioeconomic status, depression, alcohol use, medications (Yusuf et al., 2004), and environmental factors such as water hardness and climate (Nerbrand et al., 1991a; Hammar et al., 1992; Gyllerup, 2000; Hammar et al., 2001).

Fluoride may be found in drinking water naturally, or as an additive intend to provide public dental health protection (dental caries) (WHO, 2006). There is a large variation of naturally occurring fluoride in drinking water around the world, and the variation is dependent on geological factors. According to WHO, areas with naturally occurring fluoride above 1.5 mg/l are known as fluoride-endemic areas, and health effects such as dental fluorosis (a mineralization disorder of the dental enamel) is found present. Studies conducted in fluoride-endemic areas, demonstrate adverse effects from excessive drinking water fluoride exposure on the cardiovascular system. Two case-control studies in Turkey examined 63 endemic fluorosis patients and 45 matched healthy controls in order to investigate the relationship between drinking water fluoride exposure and carotid artery atherosclerosis (Varol et al., 2010a; Varol et al., 2010b). The authors conclude that excessive fluoride exposure decreased the elastic properties of ascending aorta and contributed to cardiac dysfunction. The possible mechanism, according to Varol et al. (2010b), was that inflammation and oxidative stress were induced by fluoride toxicity, but the cause for impaired aortic elastic properties is not fully understood. Further, Liu et al. (2014) performed a cross-sectional study investigating the association between excessive drinking water fluoride exposure and carotid atherosclerosis development. The study population consisted of 585 individuals living in eight villages in China, with drinking water fluoride levels ranging from <1.20 mg/l to >3.00 mg/l. A significant correlation was found between excessive fluoride exposure and prevalence of carotid artery atherosclerosis. According to the authors, the possible mechanism behind the findings was that excess fluoride induced decreasing levels of glutathione peroxidase causing the systemic inflammation and endothelial activation. The previous studies on excessive fluoride exposure suffer from methodological short-comings and the evidence is inconsistent.

The WHO (2006) report and the National Research Council (NRC) (2006) report do not address the issue of CHD and possible effects from drinking water fluoride exposure. The literature is also limited on the potential association between lower drinking water fluoride levels (i.e. <2 mg/l) and CHD. In Sweden fluoride is naturally present in the tap water, and the fluoride concentrations vary between different areas (SWWA, 2000). Previous Swedish studies have investigated the potential effect of various trace elements in the drinking water on CHD incidence and mortality, but the potential effect by fluoride has remained unclear (Nerbrand et al., 1992; Rubenowitz et al., 2000; Nerbrand et al., 2003; Rosenlund et al., 2005).

We aimed to investigate the incidence of myocardial infarction (MI) in relation to natural fluoride levels in drinking water in a large cohort of Swedish residents.

2. Methods

2.1. Study setting

All Swedish residents are assigned a unique personal identity number (PIN) that can be used for linkage of different national registers (Ludvigsson et al., 2009). Swedish health care is public and population based and hospital referrals are based on geographic residency rather than financial capacity or health insurance, ensuring an unbiased and complete ascertainment of patients receiving hospital care.

2.2. Data sources

Several nationwide registers were used and linked to identify participants and, to obtain all relevant information on outcomes and exposure. (*i*) The Total Population Register, provided by Statistics Sweden (2016) contains demographic information, such as age, sex, birth parish, domestic movements, dates of migrations, etc., on all Swedish residents and was used to identify the study cohort and also used to follow the cohort for domestic movements. Data on hospitalizations were collected from the inpatient-part of (*ii*) The National Patient Register (NPR). NPR is a nationwide population-based register, and contains information on in-hospital care since 1964 with full coverage since 1987. NPR includes information (1) the patient's PIN, (2) the date of hospital admission and discharge, (3) one primary discharge diagnosis, and up to seven additional diagnoses coded according to the Swedish contemporary version of International Classification of Disease (ICD) (ICD-7 until 1968, ICD-8 from 1968 through 1986, ICD-9 from 1986 to 1996, and ICD-10 thereafter) (The National Board of Health and Welfare, 2016b). Information on mortality was collected from (*iii*) The national Cause of Death Register (CDR) that holds information on information on the date and the primary cause of death, and the contributing causes of death, coded according to ICD (The National Board of Health and Welfare, 2016a).

2.3. Study population

Individuals born in Sweden between Jan 1, 1900 and Dec 31, 1919, alive and living in their birth parish/municipality of birth at the time of start of follow-up, were identified in the Total Population Register (n = 474.217). A total number of 18,599 individuals in the baseline cohort were excluded due to either a diagnosis of MI (identified through linkage to the NPR) prior to the time of start of follow-up (n = 4341) or due to missing fluoride exposure data (n = 14.257), thus the number of eligible individuals was 455,619.

MI was the failure event, and subjects with no MI were censored at death (n = 214.970), migration from the municipality of birth (n = 11.670), or end of follow-up (December 31, 2006; n = 24.450), whichever occurred first.

2.4. Follow-up

For each study subject follow-up started from the date the county of residence had full coverage in the NPR. All eligible individuals were followed through linkage to the NPR and the CDR to identify all individuals with a MI diagnose according to the ICD, seventh through tenth edition codes (ICD 7: 420.10:420.17; ICD 8: 410; ICD 9: 410; and ICD-10: I21.0-I22.9). All primary and additional discharge diagnoses and cause of death diagnoses were examined for the first occurrence of the outcome of interest. End of follow-up was December 31, 2006.

2.5. Exposure data

Information on drinking water fluoride and hardness measurements was provided from the Swedish Water & Wastewater Association (SWWA) which collects and evaluates data from Swedish water