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Fluoride exposure and thyroid function among adults living in Canada: Effect modification by iodine status

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ABSTRACT

Background: Fluoride exposure has the potential to disrupt thyroid functioning, though adequate iodine intake may mitigate this effect. This is the first population-based study to examine the impact of chronic low-level fluoride exposure on thyroid function, while considering iodine status. The objective of this study was to determine whether urinary iodine status modifies the effect of fluoride exposure on thyroid stimulating hormone (TSH) levels.

Methods: This cross-sectional study utilized weighted population-based data from Cycle 3 (2012 – 2013) of the Canadian Health Measures Survey (CHMS). Information was collected via a home interview and a visit to a mobile examination centre. The weighted sample represented 6,914,124 adults in Canada aged 18–79 who were not taking any thyroid-related medication. Urinary fluoride concentrations were measured in spot samples using an ion selective electrode and adjusted for specific gravity (UF_{SG}). Serum TSH levels provided a measure of thyroid function. Multivariable regression analyses examined the relationship between UF_{SG} and TSH, controlling for covariates.

Results: Approximately 17.8% of participants fell in the moderately-to-severely iodine deficient range. The mean (SD) age of the sample was 46.5 (15.6) years and the median UF_{SG} concentration was 0.74 mg/L. Among iodine deficient adults, a 1 mg/L increase in UF_{SG} was associated with a 0.35 mIU/L increase in TSH [95% CI: 0.06, 0.64; p = 0.01, one-tailed].

Conclusions: Adults living in Canada who have moderate-to-severe iodine deficiencies and higher levels of urinary fluoride may be at an increased risk for underactive thyroid gland activity.

1. Introduction

Fluoride is an element that occurs either naturally in the environment or can be industrialized and added artificially to public drinking water to protect against dental caries. Approximately 38.7% of the population in Canada receives artificially fluoridated drinking water (Public Health Capacity and Knowledge Management Unit; Quebec Region for the Office of the Chief Dental Officer of Canada, 2017a). Provinces with the highest proportion of fluoridated drinking water include: Ontario, Manitoba, and the Northwest Territories, while provinces with the lowest proportion include: the Yukon Territories, British Columbia, Newfoundland, and Quebec (Public Health Capacity and Knowledge Management Unit; Quebec Region for the Office of the Chief Dental Officer of Canada, 2017b). The recommended fluoride concentration for drinking water in Canada is 0.7 mg/L (Government of Canada, 2017). However, the national average tap water fluoride concentration in Canada, including both fluoridated and non-fluoridated regions, is 0.12 mg/L (Canadian Health Measures Survey, 2017). Fluoride exposure can also occur from tea, beverages made with fluoridated water, processed foods, dental products, supplements, pharmaceuticals, and foods sprayed with fluoride-containing pesticides.

Hypothyroidism, the most common thyroid disorder, is characterized by suppression of thyroid gland activity. Subclinical hypothyroidism is indicated by high serum thyroid stimulating hormone (TSH) concentrations of 4.5–9 mIU/L with normal triiodothyronine (T_3) and thyroxine (T_4) levels. However, TSH levels above 2.5 mIU/L may increase risk for subclinical and clinical hypothyroidism (Demers & Spencer, 2002; Waise & Price, 2009). Subclinical hypothyroidism is estimated to occur in 4.3–9.5% of the US adult population (Hollowell et al., 2002; Canaris et al., 2000) and is associated with various health

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problems (Gonzalez Gil & de la Sierra, 2017; Pesic et al., 2015; Jayasingh & Puthuran, 2016), including: miscarriage and preterm birth among pregnant women, and altered growth and neurodevelopment among offspring (Maraka et al., 2016; Zhang et al., 2017; Murphy et al., 2015; Vrijkotte et al., 2017). Moreover, "high normal" TSH levels of 2.0–4.0 mIU/L and 2.5–4.5 mIU/L have been associated with hypocholesterolemia (Michalopoulou et al., 1998), and an increased risk of metabolic syndrome (Ruhla et al., 2010) respectively. Thus, studying factors that contribute to low thyroid function, even at the subclinical level, is of high public health importance.

Animal studies have shown reductions in T_3 and T_4 levels due to fluoride exposure, even at low doses (Cinar, 2005; Bobek et al., 1976). In humans, fluoride in drinking water, even at levels as low as 0.3–0.5 mg/L, have predicted elevated TSH concentrations (Kheradpisheh et al., 2018; Bachinskii et al., 1985). Higher water fluoride concentrations have also predicted an increased likelihood of a hypothyroidism diagnosis among adults (Kheradpisheh et al., 2018; Peckham et al., 2015) and an increased incidence of diabetes among adults in the United States (Fluegge, 2016) and children in Canada (Chafe et al., 2018). However, these findings were from ecological studies and thus did not control for important confounders. Higher urinary fluoride and TSH levels have also been observed among children and adolescents living in endemic fluorosis areas (Singh et al., 2014; Khandare et al., 2018). In contrast, other studies have not found significant differences in thyroid hormone levels or thyroid disorder diagnoses as a function of urinary fluoride levels (Barberio et al., 2017).

Iodine deficiency can contribute to decreased thyroid hormone production and exacerbate the thyroid-disrupting effects of certain chemicals, as well as fluoride (Jiang et al., 2016; Yang et al., 1994; Xu & Zhang, 1994). Adequate iodine levels can offset adverse goitrogenic effects of fluoride (Xu & Zhang, 1994; Zhao et al., 1998). Fluoride exposures of 0.05–0.13 mg/kg/day have been associated with adverse thyroid effects among iodine sufficient people, while lower fluoride exposures of 0.01–0.03 mg/kg/day have been associated with these effects among iodine deficient people (National Research Council, 2006). Synergistic effects of high fluoride and deficient iodine have also been found among both animals (Zhao et al., 1998; Guan et al., 1988; Ge et al., 2005) and humans (Lin et al., 1991). Still, few studies have considered iodine as a moderator of fluoride's effects on thyroid function as large sample sizes are needed for assessment of effect modification. Cycle 2 (2009–2011) data from the CHMS indicated low iodine intakes among 22% of Canadians aged 3 to 79 (Statistics Canada, 2013; World Health Organization, 2013).

We examined whether the relationship between fluoride exposure and thyroid function is modified by iodine status among adults participating in a Canadian population-based survey. We hypothesized that higher urinary fluoride levels would predict higher TSH levels and that this relationship would be stronger among adults with moderate-to-severe iodine deficiencies.

2. Materials and methods

2.1. Participants

We utilized data from Cycle 3 of the Canadian Health Measures Survey (CHMS, 2012–2013) because it was the first cycle to include thyroid hormone measurements (data from Cycle 4 were not available at the outset of this study). The CHMS is an ongoing survey launched by Statistics Canada, Health Canada and the Public Health Agency of Canada in 2007 to collect health and wellness data and biological specimens on a nationally representative sample of Canadians. Cycle 3 was conducted between January 2012 and December 2013. It consisted of 5785 Canadians ages 3 to 79 recruited from 16 sites across all ten provinces with 2671 people providing urine and blood samples for fluoride and TSH analysis (out of the approximately 2950 who were asked to do so). People living in the three territories, on reserves or other aboriginal settlements in the provinces, full-time members of the Canadian forces, institutionalized people, and those living in remote areas were not sampled. The overall response rate for all aspects of Cycle 3 was 79% (Statistics Canada, 2015; Begin, 2015).

Information was collected from participants via a computer-assisted home interview and a visit to a mobile examination centre where biospecimens and physical measures were collected by trained professionals. Cases of hypo- or hyperthyroidism were identified from information gathered directly from the interview; participants were asked: "Remember we are interested in conditions diagnosed by a health professional … Do you have a thyroid condition?". Data on medication usage during the past month was also collected and photographs of medication bottles were obtained as part of the household questionnaire. Medication usage was later confirmed during mobile examination centre visits. This enabled identification of which participants were using thyroid or anti-thyroid medication. Individuals who were on these medications and/or reporting a thyroid condition diagnosed by a health professional were excluded from our analyses. Pregnant women were also excluded given that pregnancy may increase stress on the thyroid and demand for iodine intake. We limited our analyses to adults aged 18 and over (with urinary fluoride and TSH levels) due to the low prevalence of hypothyroidism in younger individuals. Finally, we excluded participants who had iodine levels above the WHO cut-off of 2.37 μmol/L for excess iodine levels (Iodine Status Worldwide: WHO Global Database on Iodine Deficiency, 2004). We removed these participants because excess iodine levels can cause abnormalities in TSH (Katagiri et al., 2017), including elevations, and we wanted to test the relationship between fluoride exposure and TSH as a function of iodine deficiency, not iodine excess. Approximately 1% of participants reported having kidney disease, and they were equally likely to have adequate or deficient iodine levels. Since these individuals could be particularly vulnerable to adverse effects of fluoride on the thyroid gland, we did not exclude them.

Approximately 1000 adults between the ages of 18 and 79 met the above inclusion criteria (exact number cannot be reported as per Statistics Canada reporting requirements). Using sampling weights provided by Statistics Canada, the weighted sample represented 6,914,124 adults. See Appendix A for frequencies of participants at each CHMS site according to fluoridation status.

The CHMS was approved by the Health Canada institutional review board and participants provided written informed consent. Detailed CHMS methodology has been published elsewhere (Statistics Canada, 2015; Labrecque, 2014) and full study details can be found at www.statscan.gc.ca. The present study also received ethics approval from the York University Research Ethics Board (Certificate e2018–233).

2.2. Fluoride measure

Fluoride was measured in urine which provides a valid measure of exposure given that urinary fluoride levels have been shown to directly correlate with water fluoride concentration levels in adults (Ahmed et al., 2012; Mansfield, 1999) Approximately 40% of absorbed fluoride is excreted in urine, while 60% is absorbed in calcified tissue (Barbier et al., 2010). Spot urine samples were collected under normal (not fasting) conditions and not standardized with respect to time of collection. Urinary fluoride concentrations were analyzed using an Orion PH meter with a fluoride ion selective electrode after being diluted with an ionic adjustment buffer (Institut National de Sante Publique du Quebec (INSPQ), 2009). To account for variations in urine dilution, urinary fluoride concentrations were adjusted for specific gravity (UF_{SG}; mg/L). A reference value for UF_{SG} among adults unexposed to community water fluoridation is geometric mean = 0.613 mg/L (95% CI of 0.21–1.6 mg/L) (Usuda et al., 2007). Analyses were performed at the Toxicology Laboratory of the INSPQ (accredited under ISO 17025) under standardized operating procedures (Statistics Canada, 2015). Fluoride concentrations in tap water were also measured via a basic anion exchange chromatography procedure.

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