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Threshold effects of moderately excessive fluoride exposure on children's health: A potential association between dental fluorosis and loss of excellent intelligence

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ABSTRACT

Background: Excessive fluoride exposure is associated with adverse health outcomes, but little is known of the effects of moderately chronic fluoride exposure on children's health.

Objectives: We conducted a cross-sectional study to explore the health impact of moderately excessive fluoride in drinking water.

Methods: We recruited 2886 resident children, aged 7 to 13 years, randomly from endemic and non-endemic fluorosis areas in Tianjin, China. The fluoride levels in drinking water and urine were measured using the national standardized ion selective electrode method. We examined the dose-response effects of low-to-moderate fluoride exposure on dental fluorosis (DF) and intelligence quotient (IQ), and evaluated the potential relationships between DF grades and intelligence levels using piecewise linear regression and multiple logistic regression, respectively.

Results: The adjusted odds ratios (ORs) of DF were 2.24 (95% confidence interval [CI]: 2.02 to 2.48) for every 0.1 mg/L increment in the water fluoride concentration in the range of 0.80 to 1.50 mg/L, and 2.61 (95% CI: 2.32 to 2.93) for every 0.5 mg/L increment in the urinary fluoride level up to 1.80 mg/L. Every 0.5 mg/L increment in the water fluoride level was associated with a reduction of 4.29 in the IQ score (95% CI: −8.09 to −0.48) in the range of 3.40 to 3.90 mg/L, and a decreased probability of developing excellent intelligence (IQ ≥ 130, OR = 0.60, 95% CI: 0.47 to 0.77) in the range of 0.20–1.40 mg/L, respectively. Every 0.5 mg/L increment in the urinary fluoride level was related to a decrease of 2.67 in the IQ scores (95% CI: −4.67 to −0.68) between 1.60 mg/L to 2.50 mg/L. Excellent intelligence decreased by 51% in children with higher urinary fluoride, and by 30% with each degree increment of DF.

Conclusions: Our study suggests threshold and saturation effects of moderately excessive fluoride exposure on DF and intelligence loss in children, and a potential association between DF and the loss of excellent intelligence.

1. Introduction

Fluoride is beneficial for skeletal metabolism and dental remineralization at appropriate concentrations (Do and Spencer, 2007). However, long-term ingestion of excessive amounts of fluoride can cause adverse effects on calcified tissues, principally the skeletal systems and teeth, and soft tissues such as the brain, kidneys and liver (Xiong et al., 2007). By 2016, fluoride was viewed as one of the top ten

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chemicals in terms of public health concern (Mumtaz et al., 2015). In children, one of the commonest early detrimental effects of fluoride is dental fluorosis (DF), a developmental disorder resulting in color change and hypomineralization of the enamel. The critical period for tooth development, and the formation of DF is the first 6–8 years of life, but chronic accumulation throughout the maturation stage also contributes to the severity of DF (Aoba and Fejerskov, 2002). The degree of DF is related to the fluoride concentration in drinking water and duration of consumption.

In addition to skeletal damage, the developmental neurotoxicity associated with fluoride has raised great public concern recently. Animal studies have revealed that perinatal fluoride exposure results in learning and memory impairments in rats (Dong et al., 2015; Zhu et al., 2017). Consistently, in a population-based study, children living in endemic fluorosis areas possessed lower intelligence quotient (IQ) scores than those from normal areas (Trivedi et al., 2007), suggesting an inverse association between fluoride exposure and children's intelligence. Nevertheless, another prospective study denied the correlation between early-life fluoride exposure and IQ deficits in a community water fluoridation program (Broadbent et al., 2015). Till date, the health effects of fluoride on intellectual development are inconclusive, which may be attributed to variances in the studies' sample sizes, exposure levels, study regions, demographic characteristics and other potential confounders.

Drinking water is the primary source of fluoride. Worldwide, a large proportion of individuals experiences fluorosis due to the consumption of fluoride-enriched drinking water (Meenakshi and Maheshwari, 2006). In China, approximately 87 million people from 1137 counties/districts across 28 provinces were living in the drinking-water type fluorosis areas in 2012(Lei et al., 2014); this is attributed to the high natural background and anthropogenic inputs through tannery waste, electrolysis waste and agricultural fertilizers (Ghosh et al., 2013). To diminish fluoride-related health problems, the World Health Organization (WHO) recommends a guideline value of < 1.5 mg/L of fluoride in drinking water (Indermitte et al., 2009); the guideline is stricter in China, at a fluoride value of 1.0 mg/L (Zhu et al., 2006). In the past decades, water defluoridation projects were widely implemented in areas endemic for fluorosis in China, but the fluoride concentrations in drinking water remain substandard in some areas, especially in some rural communities (Choi et al., 2012), leading to low-to-moderate fluoride exposure levels in daily life.

Although numerous studies have uncovered the harmful health effects of high-level fluoride exposure (Ayoob and Gupta, 2006), the evidence on the potentially harmful effects of chronic exposure to low-to-moderate levels of fluoride on children's dental development and intellectual performance is relatively insufficient. Importantly, it is still unknown if there exist threshold and saturation effects of fluoride exposure on DF and IQ deficit, which represent skeletal and non-skeletal damages to children's health. To address the issues, we performed a comprehensive and systematic study in a relatively large population of Chinese children to identify the association of moderately excessive fluoride exposure with DF and IQ in a dose-response pattern, and further detect the correlation between DF and IQ levels.

2. Materials and methods

2.1. Study design and population

A village-based cross-sectional study was conducted in 2015 in the rural areas of Tianjin City, China. According to the annual surveillance data from the local Center for Disease Control and Prevention (CDC), the whole district was divided into historical high fluoride areas and normal fluoride areas. The fluoride concentrations in these areas have maintained at stable levels over the past decade. None of the study sites was in the areas endemic for iodine deficiency disorders, or exposed to other potential neurotoxins like lead, arsenic or mercury. The multistage random sampling technique, stratified by area, was performed to select representative samples among local children who were permanent residents since birth. First, seven towns were selected using the simple random sampling (SRS) method, three of which were historical high fluoride areas, and four, non-endemic fluorosis areas. Then, twenty-four villages were further selected within each sample site using SRS. Finally, the cluster sampling method was applied to recruit children from each chosen village. This study was approved by the Review Board of Huazhong University of Science and Technology and Ethical Committee of Tianjin Center for Disease Control and Prevention. As all the research participants were minors, written informed consent was obtained from all the participants and their parents/guardians before study enrollment.

2.2. General data collection

Trained investigators conducted a face-to-face interview with the recruited children and their parents to collect demographic data, including age, sex, education level, physical residence, basic health status, parental occupation, socioeconomic status, and maternal adverse exposures, screening and disease history during pregnancy, as well as maternal delivery conditions. The development status of the recruited children was further assessed by the calculation of their body mass index (BMI), which was derived from their height and weight. Height (1 mm precision) was measured with a standard calibrated scale. Weight (0.1 kg precision) was measured without heavy clothing and shoes. All the measurements were conducted based on the recommended standard methods (Chandrashekar et al., 2010) by nurses. Children who had congenital or acquired diseases affecting intelligence, or a history of cerebral trauma and neurological disorders, or those with a positive screening test history (like hepatitis B virus infection, *Treponema palladium* infection and Down's syndrome) and adverse exposures (smoking and drinking) during maternal pregnancy were excluded from the analyses.

2.3. Assessment of DF

Dean's fluorosis index (WHO criteria) (Molina-Frechero et al., 2015) was used to estimate the prevalence and severity of DF. Each participant was examined by two qualified and independent experts, who had rich experience on examination of dental fluorosis. All experts were trained about the standard examination specification and the unified diagnostic criteria for dental fluorosis before the examination. The examination was performed under natural light after the vestibular surfaces of the teeth were cleaned and dried, with the assist of plane light source mirrors and CPI probes. A child's DF index was based on the most severe fluorosis form found on two or more teeth (Onoriobe et al., 2014). The DF degree was graded as normal, questionable, very mild, mild, moderate and severe. The final diagnosis was made only when judgments from the two experts were in agreement; if not, a third expert would join in and offer suggestion. For repeatability, 10% of participants were double checked and the Kappa value was 0.82.

2.4. Assessment of IQ

IQ scores were measured using the second edition of Combined Raven's Test–The Rural in China (CRT-RC2) (Liu et al., 2009) for children aged 7 to 13 years. The CRT-RC2 is a validated test for basic cognitive abilities, and has been widely adopted in China after modifications, as it is non-verbal and less affected by language, and cultural and ethnic differences (Sun et al., 2015). Briefly, it comprises 72 questions in six sets of twelve: A, AB, B, C, D and E. The CRT-RC2 was completed by each participant within 40 min according to the instruction manual. For every test, forty children were randomly allocated to one classroom to take the test independently, under the supervision of our four trained professionals. The children's IQ scores were categorized