Early Childhood Exposures to Fluorides and Child Behavioral Development and Executive Function: A Population-Based Longitudinal Study

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Abstract

It is important to both protect the healthy development and maintain the oral health of the child population. The study examined the effect of early childhood exposures to water fluoridation on measures of school-age executive functioning and emotional and behavioral development in a population-based sample. This longitudinal follow-up study used information from Australia's National Child Oral Health Study 2012–14. Children aged 5 to 10 y at baseline were contacted again after 7 to 8 y, before they had turned 18 y of age. Percent lifetime exposed to fluoridated water (%LEFW) from birth to the age 5 y was estimated from residential history and postcode-level fluoride levels in public tap water. Measures of children's emotional and behavioral development were assessed by the Strength and Difficulties Questionnaire (SDQ), and executive functioning was measured by the Behavior Rating Inventory of Executive Function (BRIEF). Multivariable regression models were generated to compare the associations between the exposure and the primary outcomes and controlled for covariates. An equivalence test was also conducted to compare the primary outcomes of those who had 100% LEFW against those with 0% LEFW. Sensitivity analysis was also conducted. A total of 2,682 children completed the SDQ and BRIEF, with mean scores of 7.0 (95% confidence interval, 6.6–7.4) and 45.3 (44.7–45.8), respectively. Those with lower %LEFW tended to have poorer scores of the SDQ and BRIEF. Multivariable regression models reported no association between exposure to fluoridated water and the SDQ and BRIEF scores. Low household income, identifying as Indigenous, and having a neurodevelopmental diagnosis were associated with poorer SDQ/BRIEF scores. An equivalence test confirmed that the SDQ/BRIEF scores among those with 100% LEFW were equivalent to that of those who had 0% LEFW. Exposure to fluoridated water during the first 5 y of life was not associated with altered measures of child emotional and behavioral development and executive functioning.

Keywords: risk and benefit balance, safety, childhood development, water fluoridation, equivalence test, Australia

Introduction

Dental caries is the most prevalent noncommunicable chronic condition in children, resulting in costly treatment and an adverse impact on quality of life (Casamassimo et al. 2009). Drinking water, diet, and use of fluoridated toothpaste are the major sources of human exposure to fluoride. Water fluoridation (WF) and the use of fluoridated toothpaste are the main preventive programs against dental caries in Australia that have been attributed with the improvement in child dental health (Ha et al. 2016; National Health and Medical Research Council [NHMRC] 2017). It is crucial to ensure its effectiveness and safety to maintain public support for this important public health program.

The developing human brain is more susceptible to injury caused by chemicals than is the mature brain (Rice and Barone 2000). In theory, chemicals can cause brain injury at levels of exposure that would have little or no adverse effect in an adult (Grandjean and Landrigan 2014). Therefore, there are concerns based on the precautionary principle that the developing human brain may be influenced by early exposure to fluoride.

A major systematic review (McDonagh et al. 2000) did not identify human studies with acceptable scientific quality to inform a view of the effect of fluoride on children's development. Another review (Choi et al. 2012) reported lower intelligence quotient (IQ) scores (7 points) in Chinese and Indian children residing in areas with very high natural fluoride levels in water (from 2 to 7.6 mg/L) than that of children in areas with

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fluoride levels of 0.5 to 1.0 mg/L. More recent systematic reviews concluded that WF is not associated with lowered intelligence (NHMRC 2017; Guth et al. 2020; Aggeborn and Öhman 2021).

Further studies since 2016 have examined the association between water fluoride levels and IQ that involved fluoride levels at or near those used in WF. A study found limited evidence of an association between urinary fluoride excretion and learning disability (Barberio et al. 2017). A Mexican study reported that maternal prenatal urinary fluoride was associated with a negative effect on intelligence in offspring aged 6 to 12 y (Bashash et al. 2017). A Swedish study found that there was no effect of fluoride in drinking water on cognitive development (Aggeborn and Öhman 2017). Studies from a Canadian cohort reported an association between maternal fluoride exposure and IQ score in offspring aged 3 to 4 y (Green et al. 2019; Till et al. 2020). These additional studies show inconsistent findings that challenge identifying evidence of an association between fluoride and child behavioral and cognitive development.

Research on the association between fluoride and child health has commonly used IQ collected in specified conditions as the outcome measure. Little is known about the association between exposure to fluoride and social, emotional, and self-regulatory behaviors and executive function of children measured in their daily environment. It is also important to investigate such an association at the population level. In previous research, the effect of low levels of lead exposure on these behaviors and functions has been assessed (Fruh et al. 2019), providing important comparative evidence for policy makers.

The study aimed to examine the effect of early childhood exposures to water fluoridation (measured as a composite index of lifetime residential history and drinking of fluoridated tap water) on measures of school-age emotional and behavioral development and executive functioning by applying a population-based cohort study design in a nationally representative sample.

Methods

We used a longitudinal population-based research design to pursue the aims. The study sample of the Australia's National Child Oral Health Study (NCOHS) 2012–14 (Do and Spencer 2016) served as the framework for this study. NCOHS was a large population-based study of schoolchildren across Australia with a multistage, stratified random sample selection process to ensure its population representativeness. Some 24,664 study participants aged 5 to 14 y had both questionnaire and oral examination data (Do and Spencer 2016). In total, 15,793 of those served as the baseline sample because they were born during 2001 to 2008 and, hence, were under the age of 18 y when the follow-up study was conducted. NCOHS data have been used to investigate the association between WF and dental caries (Spencer et al. 2018).

Parents of NCOHS participants younger than 18 y at the time of this follow-up (2018–19) were sent an email containing a Participant Information Sheet, an invitation letter, and a link to an online version of the study questionnaire. Nonrespondents were also posted a study package including a paper version of the questionnaire via the address obtained at the baseline. If again this received no response, participants were contacted via telephone available from the baseline. Up to 6 approaches were conducted.

The Main Exposure

The NCOHS questionnaire collected a detailed residential history from birth of the children to the time of the baseline survey and included consumption of public water. Parents were asked to report drinking of public water by the child and use of any water filters that remove fluoride for each of the reported residences. We used a comprehensive database of postcode-level fluoride levels in public water supplies since the 1990s (Do and Spencer 2007). The residential history of NCOHS participants has been linked with the postcode-level fluoride concentration database to allow calculation of the individual-level percentage of lifetime exposure to fluoridated water (%LEFW) (Do and Spencer 2007). For this research, %LEFW from birth to age 5 y (the youngest age of those surveyed at baseline) was used to form 3 groups of participants: having 0%, >0% to <100%, and 100% LEFW.

Primary Outcome Measures of Child Behavioral Development and Executive Function

We used the Strength and Difficulties Questionnaire (SDQ) (Goodman 2001) to measure emotional and behavioral development and the Behavior Rating Inventory of Executive Function (BRIEF) (Gioia et al. 2000) to measure child executive functioning.

The SDQ has been extensively validated as a measure of emotional and behavioral development among population-based and clinical samples of children aged 4 to 17 y. The 25-item scale is completed by parents and has 5 subscales measuring different aspects of emotional and behavioral development, including emotional symptoms, conduct problems, hyperactivity, peer problems, and prosocial skills. The SDQ has been used widely in population health surveys as a gold standard for assessing child emotional and behavioral development (Sawyer et al. 2015). A Total Difficulties Score (TDS) is generated by adding scores from all the scales (excluding prosocial behavior) and ranges from 0 to 40. Higher scores on the SDQ indicate a higher risk of psychosocial or mental health problems. A TDS score of 16 is considered an appropriate cut point for clinically significant mental health in population samples (Aoki et al. 2021). Hence, the SDQ TDS score was analyzed as a continuous variable, together with a dichotomized variable (SDQ16+). License for use of SDQ in this study was purchased from Youthinmind Ltd.

The BRIEF comprises 8 scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor), which are combined to provide a Global Executive Composite for children aged 5 to

18 y. The BRIEF scores are age- and gender-standardized, and higher scores reflect greater executive functioning difficulties. The scale has been found to have good internal consistency and test–retest reliability, as well as clinical validity (Gioia et al. 2000). Executive functioning is an important indicator of child cognitive development. *T* scores are used to interpret the child's level of executive functioning as reported by the parents on the BRIEF questionnaire. The *T* scores are linear transformations of the raw scale scores (mean Global Executive Composite [GEC] *T* score = 50, SD = 10) and provide information about a child's scores relative to the scores of children in the standardization sample. Higher scores on the BRIEF (with GEC *T* scores ≥65) indicate a greater level of dysfunction in a specific domain of executive function (Gioia et al. 2000). Hence, the BRIEF GEC *T* score was analyzed as a continuous variable, together with a dichotomized variable (GEC65+). License for use of BRIEF was purchased from Psychological Assessment Resources.

Other Covariates

Covariates used in the multivariable regression models were selected as potentially influencing the association between fluoride exposure and the outcomes. Covariates were child's age at follow-up, sex and Indigenous identity, household income, parental education and country of birth, area-level remoteness status, neurodevelopmental diagnosis, breastfeeding and toothbrushing with fluoride toothpaste in early childhood (see the Appendix).

Statistical Analysis

We managed and analyzed data with SAS 9.4 (SAS Institute) and SAS-callable SUDAAN 11.3. Data collected in the follow-up questionnaire were merged with the NCOHS baseline data using individual unique identifiers. The SDQ TDS and the BRIEF GEC and their respective subscale scores were calculated based on the test manuals of the instruments.

All the analyses used SUDAAN complex sampling procedures to account for stratified sampling and clustering within areas. Mean and 95% confidence interval (CI) of the SDQ TDS and BRIEF GEC, as well as prevalence and 95% CI of SDQ16+ and GEC65+, were calculated for the exposure groups and covariates. Analyses were weighted to represent the target population. We conducted generalized linear regression models for the SDQ TDS and BRIEF GEC scores to estimate β coefficients of categories against the reference of each variable. Similarly, log-Poisson regression models with robust standard error estimation were generated for the prevalence of SDQ16+ and GEC65+ to estimate adjusted prevalence ratios (PR).

For sensitivity analysis, respective multivariable models were generated for SDQ TDS and BRIEF GEC stratified by sex and by neurodevelopmental diagnosis. Subscale scores of SDQ and BRIEF were also analyzed. Multiple imputation for missing data of covariates was also conducted (see the Appendix).

We tested the hypothesis of noninferiority between the groups by exposure to fluoride following standard approaches (Fleming 2008; Scott 2009; Schumi and Wittes 2011). We hypothesized that indicators of child health and development associated with exposure to water fluoridation would be noninferior to that associated with no exposure to WF by more than a clinically acceptable equivalence margin Δ (Fleming 2008; Scott 2009). This hypothesis was a more appropriate approach because the traditional null hypothesis of no difference cannot provide proof of similarity (Scott 2009; Schumi and Wittes 2011). This is an important principle in evaluating risk-benefit profiles of public health programs (Barker et al. 2002). We defined the equivalence margin Δ for SDQ TDS and BRIEF GEC as 1/8 of the standard deviation of their population norms. We then tested the estimated SDQ TDS and BRIEF GEC scores and their 95% CI bounds against the predetermined equivalence margins Δ for each outcome to test the study's hypothesis.

The study has received ethical approval from the University of Adelaide and the University of Queensland Human Research Ethics Committees. The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines for observational human research.

Results

A total of 2,682 (17%) participants completed the SDQ and BRIEF in the follow-up questionnaire (Table 1). The retention rate of the follow-up sample was associated with %LEFW, parental education, and household income. The retention rates were relatively higher among those with 100% LEFW, those whose parents had a tertiary education, and those with high household income compared with their respective counterparts. Some 11% of the follow-up sample reportedly had at least 1 neurodevelopmental diagnosis.

The mean SDQ TDS score was 7.0, with some 8% of the sample having a TDS score of 16+ (Table 2). The BRIEF GEC mean score was 45.3, with 4.6% of the sample having a GEC score of 65+. The SDQ TDS and BRIEF GEC scores were similar between groups by exposure to fluoridated water. Both means of SDQ TDS and BRIEF GEC and prevalence of SDQ16+ and GEC65+ were significantly associated with parental education and household income. Children of the lower socioeconomic groups defined by parental education and household income had higher mean scores of those indicators and prevalence of scores in the "clinical" range. Children who reportedly had a neurodevelopmental diagnosis had higher mean scores of SDQ TDS and BRIEF GEC. The prevalence of SDQ16+ and GEC65+ was some 5 times higher in those with a neurodevelopmental diagnosis than those without.

Estimates of the 4 multivariable regression models for the indicators of executive functioning and emotional and behavioral development are presented (Tables 3 and 4). Against the 100% LEFW group, those with 0% LEFW had comparable estimates of SDQ TDS and BRIEF GEC. Those with 0% LEFW had higher adjusted PRs of SDQ TDS of 16+ and

Table 1. Study Sample Characteristics (Follow-up Sample *n* = 2,682).

Characteristic	Follow-up Sample	Baseline Sample
	Weight % (95% CI)	Weight % (95% CI)
% Lifetime exposure to fluoridated water, *n* = 2,535		
0%	24.7 (21.9–27.8)	33.5 (30.7–36.3)
>0% to <100%	18.0 (15.9–20.3)	17.5 (16.5–18.6)
100%	57.3 (53.5–60.9)	49.0 (46.0–52.0)
Sex, n = 2,682		
Male	47.4 (43.0–50.0)	51.5 (50.2–52.8)
Female	52.6 (49.0–56.0)	48.5 (47.2–49.8)
Parental education, *n* = 2,581		
School only	14.6 (12.5–17.0)	29.5 (27.7–31.4)
Vocational	20.2 (17.5–23.1)	21.8 (20.5–23.1)
Tertiary	65.2 (61.6–68.6)	48.7 (46.4–51.0)
Household income, *n* = 2,576		
Low	18.5 (16.1–21.1)	32.3 (30.1–34.6)
Medium	39.1 (35.8–42.5)	38.3 (36.7–39.9)
High	42.4 (38.6–46.3)	29.4 (27.2–31.7)
Parent country of birth, *n* = 2,670		
Other	34.7 (31.9–37.5)	36.5 (34.4–38.6)
Australia	65.3 (62.5–68.1)	63.5 (61.4–65.6)
Indigenous identity, *n* = 2,668		
Indigenous	2.0 (1.3–2.9)	5.8 (4.9–6.9)
Non-Indigenous	98.0 (97.1–98.7)	94.2 (93.1–95.1)
Residential location, *n* = 2,682		
Outer regional/remote and very remote	11.1 (9.0–13.6)	12.1 (10.0–14.5)
Inner regional	19.4 (16.1–23.0)	19.7 (16.9–22.8)
Major city	69.5 (65.7–73.1)	68.2 (64.6–71.6)
Breastfeeding duration, *n* = 2,633		
Never breastfed	16.1 (14.1–18.3)	24.9 (23.5–26.4)
Breastfed to 6 mo	33.3 (30.4–36.2)	34.7 (33.3–36.0)
Breastfed 6 to 24 mo	44.5 (41.4–47.7)	34.1 (32.4–35.9)
Breastfed 24+ mo	6.1 (5.0–7.5)	6.3 (5.7–6.9)
Toothbrushing frequency, *n* = 2,554		
<2 times/d	27.1 (24.3–30.1)	31.7 (30.2–33.3)
2+ times/d	72.9 (69.9–75.7)	68.3 (66.7–68.8)
Neurodevelopmental diagnosis, *n* = 2,682		
Yes	11.9 (10.1–14.0)	NA
No	88.1 (86.0–89.9)	NA

Baseline sample: The study sample of the National Child Oral Health Study (NCOHS) 2012–14 who were born during 2001 to 2008, *n* = 15,793.
Follow-up sample: The sample of NCOHS 2012–14 sample who were born during 2001 to 2008 and have complete data for the follow-up 2019–20.
Neurodevelopmental diagnosis: Study participants who reportedly had at least 1 diagnosed condition (attention-deficit disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder, dyslexia, dyscalculia). Toothbrushing frequency: Frequency of toothbrushing with fluoride toothpaste at the age of 2 y per day.
CI, confidence interval; NA, not available.

BRIEF GEC of 65+ than the 100% LEFW group, but the 95% CIs of the estimates contained 1.

The adjusted estimates of the mean scores of SDQ TDS and BRIEF GEC were associated with household income, Indigenous identity, and neurodevelopmental diagnosis (Table 3). The prevalence of SDQ16+ and GEC65+ was also associated with those factors as well as with parental education (Table 4). Children in the low socioeconomic groups had poorer indicators of executive functioning and emotional and behavioral development than their counterparts. Those who reportedly had a neurodevelopmental diagnosis had considerably poorer indicators of executive functioning and emotional and behavioral development than those without.

The sensitivity analyses stratified by sex and by having neurodevelopmental diagnosis and SDQ and BRIEF subscale analyses show that there was no association between %LEFW and the indicators of executive functioning and emotional and behavioral development (see the Appendix).

The predicted marginal estimates of the mean SDQ TDS score of the 100% LEFW group were plotted against the estimate of the 0% LEFW and the lower and upper equivalence margins Δ for SDQ TDS (Fig.). The lower 95% CIs of the estimate of the 100% LEFW group were lower than the lower bound of the equivalence margins ($-\Delta$), while the upper 95% CI bound was lower than the upper Δ. This is equivalent to scenario B, "noninferiority shown," of possible scenarios of equivalence test (Scott 2009; Schumi and Wittes 2011).

Similarly, the predicted marginal estimate of the mean BRIEF GEC score of the 100% LEFW group was plotted against the estimate of the 0% LEFW and the lower and upper

Table 2. SDQ and BRIEF Scores by Study Sample Characteristics and Covariates.

	SDQ Total Score		BRIEF	
Characteristic	Mean (95% CI)	% SDQ16+ (95% CI)	Mean (95% CI)	% GEC65+ (95% CI)
Total	7.0 (6.6–7.4)	8.0 (6.5–9.9)	45.3 (44.7–45.8)	4.6 (3.6–5.9)
% Lifetime exposure to fluoridated water				
0%	7.6 (6.8–8.4)	11.5 (8.2–16.0)	45.8 (44.7–46.9)	6.3 (4.2–9.4)
>0% to <100%	7.0 (6.1–7.8)	8.3 (4.2–15.7)	45.5 (44.4–46.7)	4.3 (2.5–7.5)
100%	6.7 (6.1–7.2)	6.4 (4.8–8.6)	44.9 (44.2–45.6)	3.8 (2.6–5.5)
Sex				
Male	6.6 (6.1–7.1)	6.0 (4.5–8.0)	44.3 (43.7–44.9)	3.3 (2.1–5.0)
Female	7.3 (6.8–7.9)	9.9 (7.4–13.0)	46.1 (45.3–46.9)	5.8 (4.3–7.8)
Parental education				
School only	8.5 (7.3–9.7)	14.8 (10.0–21.3)	46.8 (45.3–48.4)	8.8 (5.4–14.1)
Vocational	8.0 (7.1–8.9)	10.9 (7.3–15.9)	46.7 (45.4–48.1)	7.5 (4.6–12.0)
Tertiary	6.3 (5.9–6.7)	5.8 (4.1–8.0)	44.4 (43.8–45.0)	2.8 (1.9–4.0)
Household income				
Low	9.7 (8.8–10.6)	17.3 (12.6–23.4)	48.1 (46.8–49.4)	9.1 (6.0–13.4)
Medium	6.9 (6.5–7.4)	7.6 (5.6–10.2)	45.2 (44.4–45.9)	4.6 (3.1–6.9)
High	5.9 (5.3–6.5)	5.1 (3.1–8.4)	44.1 (43.3–45.0)	2.9 (1.8–4.8)
Parent country of birth				
Other	7.0 (6.4–7.6)	9.4 (6.3–13.7)	44.9 (44.0–45.8)	4.2 (2.6–6.7)
Australia	7.0 (6.6–7.5)	7.3 (5.8–9.3)	45.4 (44.8–46.1)	4.9 (3.6–6.5)
Indigenous identity				
Indigenous	12.4 (8.4–16.4)	31.3 (15.4–53.3)	52.0 (47.9–56.1)	19.3 (9.4–35.4)
Non-Indigenous	6.9 (6.5–7.3)	7.6 (6.1–9.5)	45.1 (44.6–45.6)	4.3 (3.3–5.6)
Residential location				
Outer regional/remote and very remote	7.7 (6.8–8.6)	9.5 (6.6–13.6)	46.0 (44.9–47.2)	7.3 (4.6–11.5)
Inner regional	8.0 (7.1–8.9)	11.3 (8.0–15.7)	46.6 (45.5–47.8)	6.1 (3.9–9.4)
Major city	6.6 (6.1–7.1)	6.9 (5.0–9.3)	44.7 (44.1–45.4)	3.8 (2.7–5.3)
Breastfeeding duration				
Never breastfed	8.2 (7.1–9.3)	15.7 (10.5–22.7)	46.0 (44.6–47.4)	6.7 (4.0–11.0)
Breastfed to 6 mo	6.8 (6.2–7.5)	7.3 (4.5–11.6)	44.7 (43.8–45.7)	3.7 (2.3–5.9)
Breastfed 6 to 24 mo	6.6 (6.1–7.1)	7.1 (5.1–9.9)	45.3 (44.5–46.0)	4.2 (2.9–6.2)
Breastfed 24+ mo	7.4 (6.0–8.7)	7.6 (3.6–15.3)	46.0 (44.1–47.9)	6.4 (2.7–14.4)
Toothbrushing frequency				
<2 times/d	7.3 (6.7–8.0)	8.8 (6.3–12.1)	45.5 (44.6–46.3)	4.4 (3.1–6.3)
2+ times/d	6.6 (6.1–7.1)	7.6 (5.8–9.9)	44.9 (44.2–45.6)	4.6 (3.3–6.5)
Neurodevelopmental diagnosis				
Yes	13.3 (11.9–14.9)	32.9 (25.8–40.8)	51.2 (49.7–52.7)	22.6 (16.7–29.8)
No	6.1 (5.8–6.5)	4.6 (3.3–6.5)	43.7 (43.2–44.2)	2.2 (1.5–3.3)

For the SDQ and BRIEF, lower scores are better.
BRIEF, Behavior Rating Inventory of Executive Function; CI, confidence interval; GEC, Global Executive Composite; GEC65+, Global Executive Composite group with BRIEF total score of 65 or higher; SDQ, Strength and Difficulties Questionnaire; SDQ16+, group with Strength and Difficulties Questionnaire total score of 16 or higher.

equivalence margins Δ for BRIEF GEC (Fig.). The 95% CIs of the estimate were within the bounds of the lower and upper equivalence margins. This scenario demonstrates an equivalence between the 2 groups.

Discussion

This longitudinal population-based study aimed to investigate the potential effect of exposure to fluoridated water in early childhood on child emotional and behavioral development and executive functioning. The study has consistently demonstrated that exposure to fluoridated water by young Australian children was not associated with those important developmental functions. The indicators of 2 widely validated measures of emotional and behavioral development and executive functioning among those Australian children who had whole lifetime exposure to fluoridated water were at least equivalent to those of children who did not have any exposure to fluoridated water.

To our knowledge, this study is the first to investigate an association between exposure to fluoridated water and measures of executive function and behavioral development in a national representative study sample. Executive functioning and emotional and behavioral development are key aspects of childhood development and daily life (Diamond 2013). Those aspects are affected by chemical injury to the developing brain.

Table 3. Multivariable Regression Models for SDQ TDS and BRIEF GEC Scores.

	SDQ TDS (*n* = 2,144)	BRIEF GEC (*n* = 2,267)
Characteristic	β (95% CI)	β (95% CI)
Intercept	4.04 (3.03–5.04)	41.81 (40.20–43.43)
% Lifetime exposure to fluoridated water		
0%	0.41 (−0.49 to 1.30)	0.34 (−1.01 to 1.69)
>0% to <100%	0.23 (−0.93 to 1.39)	0.55 (−1.06 to 2.16)
100%	Reference	Reference
Sex		
Male	−0.05 (−0.78 to 0.69)	−0.83 (−1.97 to 0.16)
Female	Reference	Reference
Parental education		
School only	0.62 (−0.42 to 1.66)	1.03 (−0.68 to 2.75)
Vocational	0.96 (−0.18 to 2.10)	2.06 (0.41–3.71)
Tertiary	Reference	Reference
Household income		
Low	2.14 (1.03–3.25)	1.95 (0.30–3.59)
Medium	0.73 (−0.07 to 1.53)	0.55 (−1.06 to 2.16)
High	Reference	Reference
Parent country of birth		
Other	0.85 (0.02–1.67)	0.84 (−0.42 to 2.11)
Australia	Reference	Reference
Indigenous identity		
Indigenous	3.85 (1.06–6.65)	4.10 (0.85–7.35)
Australia	Reference	Reference
Residential location		
Outer regional/remote and very remote	0.23 (−0.80 to 1.25)	0.21 (−1.37 to 1.78)
Inner regional	0.50 (−0.47 to 1.46)	1.07 (−0.35 to 2.50)
Major city	Reference	Reference
Breastfeeding duration		
Never breastfed	0.60 (−0.54 to 1.75)	0.42 (−1.20 to 2.04)
Breastfed 6 to 24 mo	0.18 (−0.63 to 1.00)	1.05 (−0.15 to 2.25)
Breastfed 24+ mo	0.64 (−0.83 to 2.11)	1.94 (−0.28 to 4.17)
Breastfed to 6 mo	Reference	Reference
Toothbrushing frequency		
<2 times/d	0.53 (−0.17 to 1.23)	0.15 (−0.93 to 1.22)
2+ times/d	Reference	Reference
Neurodevelopmental diagnosis		
Yes	7.13 (5.69–8.56)	10.25 (7.75–12.76)
No	Reference	Reference

Beta coefficient (β), relative to the reference group, was estimated by multivariable generalized linear regression models with robust standard error estimation using SAS-callable SUDAAN PROC REGRESS. Multivariable regression models controlled for all the reported variables and age at follow-up. BRIEF, Behavior Rating Inventory of Executive Function; CI, confidence interval; GEC, Global Executive Composite; SDQ, Strength and Difficulties Questionnaire; TDS, Total Difficulties Score.

In a recent study of the effect of lead at a level even lower than the Centers for Disease Control and Prevention (CDC) reference level of 5 μg/dL in whole blood, effects of lead exposure on child emotion and behaviors and executive functioning were detected (Fruh et al. 2019). Similar associations were reported between early life exposure to per- and polyfluoroalkyl substances (PFAS) and child emotion and behaviors and executive functioning (Stein et al. 2014; Harris et al. 2021). Given the uncertainty in evidence of the association between exposure to fluoridated water and child development, any research on such an association should target primary outcomes of child development that are sensitive to even small chemical injury and use instruments that can reliably measure those outcomes. The 2 instruments used in this study (SDQ and BRIEF) have shown high reliability in measuring those aspects (Nyongesa et al. 2019; Thompson et al. 2021). Hence, the study contributes to addressing the call to investigate the potential neurotoxic effect of fluoride (Bellinger 2019).

Our study findings were consistent with recent major systematic reviews (NHMRC 2017; Guth et al. 2020; Aggeborn and Öhman 2021), which concluded no association between water fluoridation and the cognitive function of children or adults. An earlier systematic review by UK Medical Research Council (McDonagh et al. 2000) concluded that there was no clear evidence of potential adverse effects other than dental fluorosis.

Several recent individual studies using IQ reported varying findings. A study in Mexico reported no association between

Table 4. Multivariable Regression Models for the Prevalence of Clinically High Scores of the Strength and Difficulties Questionnaire and Behavior Rating Inventory of Executive Function.

	% SDQ16 (*n* = 2,144)	% GEC65+ (*n* = 2,267)
Characteristic	PR (95% CI)	PR (95% CI)
% Lifetime exposure to fluoridated water		
0%	1.77 (1.03–3.05)	1.24 (0.64–2.40)
>0% to <100%	1.33 (0.53–3.33)	0.98 (0.46–2.09)
100%	Reference	Reference
Sex		
Male	1.02 (0.62–1.68)	0.87 (0.48–1.60)
Female	Reference	Reference
Parental education		
School only	1.52 (0.58–2.62)	1.99 (0.84–4.71)
Vocational	1.47 (0.88–2.74)	2.35 (1.21–4.55)
Tertiary	Reference	Reference
Household income		
Low	1.48 (0.79–2.81)	1.21 (0.53–2.76)
Medium	1.19 (0.68–2.07)	1.09 (0.53–2.22)
High	Reference	Reference
Parent country of birth		
Other	1.95 (1.26–3.01)	1.56 (0.86–2.84)
Australia	Reference	Reference
Indigenous identity		
Indigenous	1.92 (1.05–3.49)	1.59 (0.45–5.58)
Australia	Reference	Reference
Residential location		
Outer regional/remote and very remote	1.00 (0.55–1.82)	1.08 (0.48–2.41)
Inner regional	1.07 (0.63–1.82)	1.04 (0.48–2.26)
Major city	Reference	Reference
Breastfeeding duration		
Never breastfed	1.12 (0.66–1.89)	1.36 (0.62–2.97)
Breastfed 6 to 24 mo	0.89 (0.50–1.58)	1.41 (0.74–2.70)
Breastfed 24+ mo	1.11 (0.49–2.52)	2.58 (1.05–6.33)
Breastfed to 6 mo	Reference	Reference
Toothbrushing frequency		
<2 times/d	1.01 (0.68–1.52)	0.72 (0.41–1.28)
2+ times/d	Reference	Reference
Neurodevelopmental diagnosis		
Yes	6.81 (4.25–10.89)	9.59 (5.17–17.79)
No	Reference	Reference

Multivariable regression models controlled for all the reported variables and age at follow-up.
CI, confidence interval; GEC65+, Global Executive Composite group with Behavior Rating Inventory of Executive Function total score of 65 or higher; PR, prevalence ratio relative to the reference group, estimated by multivariable log-binomial models with robust standard error estimation using SAS-callable SUDAAN PROC LOGLINK; SDQ16+, group with Strength and Difficulties Questionnaire total score of 16 or higher.

IQ score measured by Raven's Coloured Progressive Matrices and fluoride exposure level (Soto-Barreras et al. 2019). A study in Spain reported that maternal fluoride levels were associated with better cognitive scores in childhood (Ibarluzea et al. 2022). A study from Canada reported an association between measures of fluoride exposure and the hyperactivity/inattention subscale score of the SDQ but not with the TDS or other subscale scores (Riddell et al. 2019). We did not find any association between all subscale scores and fluoride exposure. The Green et al. study (Green et al. 2019) reported an association among boys but not among girls. We did not find any association in the whole sample as well as among males and females separately. The Till et al. study (Till et al. 2020), using data from the same sample, reported an association between Performance IQ and infant formula use. Such association might also be explained by the strong effect of breastfeeding duration on IQ, as reported in a population-based birth cohort study sample in Denmark, which is not fluoridated (Mortensen et al. 2002). Many biological and social factors can cause large IQ differences (Nisbett et al. 2012). Even in the same household, Kristensen and Bjerkedal reported a difference in IQ of 3 points in early adulthood favoring firstborn children over later-born children (Kristensen and Bjerkedal 2007).

A feature of our study is the use of equivalence tests to investigate an association between fluoride exposure and the primary outcomes. We aim to investigate if early life exposure to fluoride altered the normal childhood development. Water fluoridation is effective in preventing dental caries in children

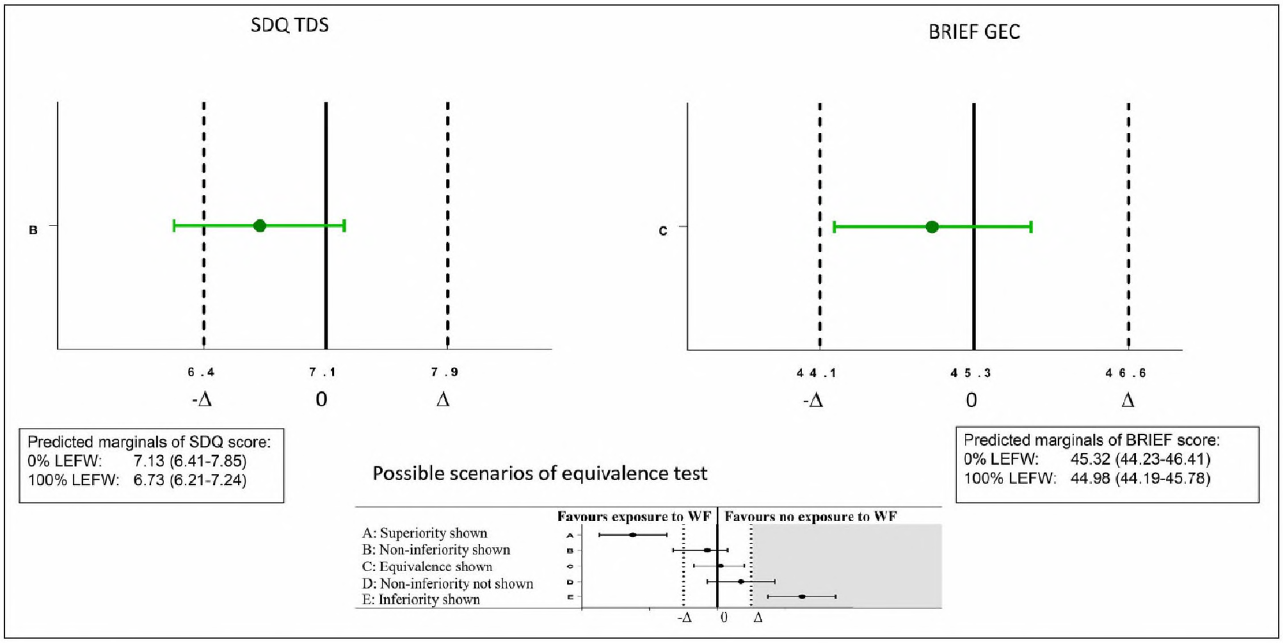

Figure. Equivalence test of Strength and Difficulties Questionnaire Total Difficulties Score (SDQ TDS) and Behavior Rating Inventory of Executive Function Global Executive Composite (BRIEF GEC) score. LEFW, lifetime exposed to fluoridated water; WF, water fluoridation.

(NHMRC 2017; McDonagh et al. 2000). An important research question remains about potential risks of early life exposures to fluoride. To have an acceptable risk/benefit balance, preventive programs must not alter the normal development of children. In other words, their effects on cognitive and behavioral development of children must be equivalent/noninferior to that observed in children who do not have early life exposures to fluoride. Therefore, the burden of proof lies with an alternative hypothesis that the population means are equivalent/noninferior. Such evidence can be provided with a test of equivalence/noninferiority, as used in our study.

A strength of this study is its population representativeness. The baseline NCOHS study sample was randomly selected to represent the Australian child population at the time. This follow-up study targeted the whole NCOHS sample aged 5 to 10 y at baseline. While there were variations in retention rates, our investigation confirmed that those variations did not confound the association between the exposure and the outcomes. The directions of the associations between the exposure and the SDQ and BRIEF scores were highly consistent with each other, further confirming the overall conclusion of the study. The directions of the associations between covariates (neurodevelopmental diagnosis, parental education, household income, and Indigenous status) and the primary outcomes were as expected. The residential history was collected from parental responses, which might be subject to recall error. It is believed that residential location at birth and during the first few years of life of children up to the age of 10 y at baseline could be easily recalled. Our equivalence test focused on children having 2 absolutely opposite levels of exposure to fluoridated water. The equivalence margins Δ were clinically small (one-eighth of the standard deviation of the respective population norms of the SDQ and BRIEF). Despite that, the outcome measures of child behavioral and emotional development and executive functioning of those contrasting groups were still equivalent.

Conclusion

This nationwide population-based follow-up study has provided consistent evidence that exposure to fluoridated water by young children was not negatively associated with child emotional, behavioral development, and executive functioning in their adolescent years. Children who had been exposed to fluoridated water for their whole early childhood had their measures of emotional, behavioral development, and executive functioning at least equivalent to that of children who had no exposure to fluoridated water.

Author Contributions

L.G. Do, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; A.J. Spencer, contributed to conception, design, data acquisition and interpretation, critically revised the manuscript; A. Sawyer, A. Jones, S. Leary, contributed to conception, design and data interpretation, critically revised the manuscript; R. Roberts, data acquisition and interpretation, critically revised the manuscript; D.H. Ha, contributed to conception, design, data acquisition, analysis, and interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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