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Tooth decay prevention and neurodevelopmental disorder risk following childhood fluoride exposure

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Abstract

Background The Centers for Disease Control and Prevention (CDC) reports that water fluoridation is among the ten greatest public health achievements of the 20th Century. Tooth decay (TD) prevention and neurodevelopmental disorder (ND) risk were assessed in relation to childhood water fluoridation exposure.

Methods This longitudinal cohort study examined the Independent Healthcare Research Database (IHRD) composed of prospectively collected healthcare data from the Florida Medicaid system for the period 1990–2012, using logistic and frequency statistical modeling (with adjustment for covariates). A cohort of 73,254 children continuously enrolled for their first 10 years of life was examined. The yearly percentage of persons in Florida receiving fluoridated water exposure from community water systems was examined by county. The number of children diagnosed with TD, autism spectrum disorder (ASD), attention deficit-hyperactivity disorder (ADHD), intellectual disability (ID), and specific delays in development (SDD) was evaluated.

Results Fluoride exposure in the year of birth, statistically significantly and dose-dependently, slightly reduced the risk of TD, and, separately, slightly increased the risk of ASD, ADHD, ID, and SDD. During the first 10 years of life, children who were fluoride-exposed as compared to unexposed were at significantly lower risk for TD, and, separately, at significantly greater risk for ASD, ID, and SDD.

Conclusions Findings from the present study, coupled with previous studies, suggest new risk/benefit analyses of water fluoridation should be undertaken.

Keywords Autistic, Asperger's disorder, Cavities, Development delay, Fluoride, Learning disabilities, Neurotoxicology

Background

The United States (US) Centers for Disease Control and Prevention (CDC) reported that the fluoridation of drinking water was among the ten greatest US public health achievements of the 20th Century [1]. Fluoridation of drinking water in the US began in 1945 and by the end of the century reached an estimated 144 million persons [1]. Water fluoridation safely and inexpensively reduces dental caries (40%−70% reduction in tooth decay (TD)) regardless of socioeconomic status or access to care [1]. According to the US CDC, since 1950, opponents of water fluoridation have claimed that it increases the risk for cancer, Down's syndrome, heart disease, osteoporosis and bone fracture, acquired immunodeficiency syndrome, low intelligence quotient (IQ), Alzheimer's disease, allergic reactions, and other health conditions [2]. The US CDC maintains water fluoridation safety is re-evaluated frequently, and no credible evidence supports an association between fluoridation and any of these conditions [2].

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Despite reassurances from the US CDC regarding the safety and effectiveness of water fluoridation, recent data suggests the importance of undertaking further research to examine the accuracy of this stance.

In 2024, the Cochrane Review undertook an exhaustive consideration of studies examining the prevention of childhood dental caries by water fluoridation [3]. These investigators concluded, based upon contemporary studies, that initiation of water fluoridation might lead to a slight increase in the proportion of caries-free children, but with smaller effect sizes than pre-1975 studies. They also concluded that there was insufficient evidence to determine the effect of water fluoridation cessation on caries and, in addition, to determine whether water fluoridation resulted in a change in disparities in caries according to socioeconomic status.

The US National Research Council of the US National Academy of Sciences also examined water fluoridation safety [4]. They concluded that fluoride through both direct and indirect mechanisms can adversely affect the brain, and recommended additional research to assess water fluoride safety. A subsequent comprehensive review supported a significant association between elevated fluoride intake during early development and neurotoxicity [5].

The purpose of this multi-decade, large population-based, hypothesis-testing epidemiological study is to further examine the safety and efficacy of water fluoridation. The aim of the current study seeks to determine TD prevention and neurodevelopmental disorder (ND) risk following routine childhood water fluoride exposure among American children.

Methods

Independent Healthcare Research Database (IHRD)

The Independent Healthcare Research Database (IHRD) was examined in this study. The IHRD, as described in numerous previous studies [6–10], is composed of de-identified, linkable (using a unique identifier code) healthcare records generated from the Florida Medicaid system from July 1990 through June 2012. Eligibility and Claim files were obtained from the Agency for Health Care Administration of the state of Florida and utilized to create the IHRD. The IHRD contains detailed person-specific demographic and diagnostic (using the International Code for Disease, 9th revision (ICD-9) codes) data. IHRD data were assembled and accessed under approval by the Liberty Institutional Review Board (Deland, FL). The SAS system for Windows, version 9.4 (Cary, NC, USA) was used in this study.

Study participants

Figure 1 presents a flowchart of the IHRD data examined. A cohort of 9,358,645 persons of all ages with eligibility at specific times for Florida Medicaid was initially evaluated. A total of 495,306 persons were continuously eligible for Florida Medicaid for 120 months during which time they made ≥ 10 outpatient office visits. Among these persons, a total of 134,388 children were enrolled from birth. Further, by specifying that each child reside in the same county during their enrollment period and have a known race and gender, a total of 73,254 children remained in the cohort examined. Finally, from the overall cohort, subcohorts of children continuously fluoride-exposed during their enrollment period (n = 25,662) and children continuously fluoride-unexposed during their enrollment period (n = 2,509) were examined.

Estimated fluoridated water exposure

Detailed data accumulated by the Public Health Dental Program of Florida was accessed online using the Florida Health Charts portal to determine child-specific fluoride exposures [11]. The accessed data estimates the percentage of Florida populations receiving fluoridated water supplies by year and by county (there are a total of 67 counties). To determine yearly and county specific

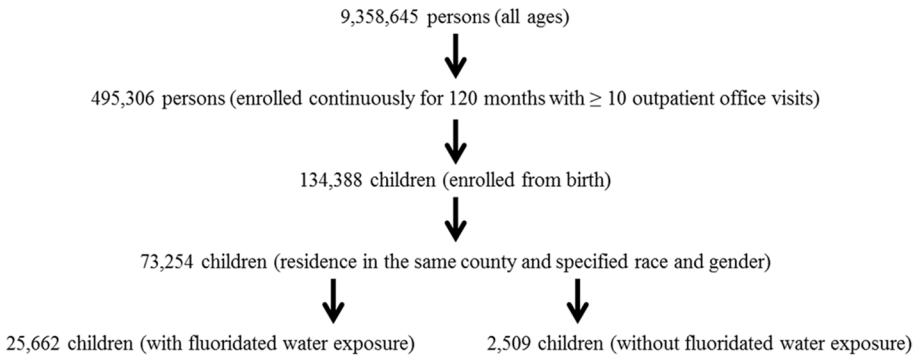

Fig. 1 A flowchart of the data examined in this study

fluoridated water exposure (the percentage of the persons served by fluoridated water), the number of people on community water systems receiving fluoridated water was divided by the number of people on community water systems on a yearly basis for each Florida county.

The percentage of persons receiving fluoridated water exposure in a given Florida county and year were then cross-linked into the IHRD data for each child's year and county of birth. Then, this same procedure was undertaken for each subsequent year of enrollment through age 10. Thus, each child had an annual estimated water fluoride exposure value from 0 to 100% for each year of enrollment between birth and 10 years of age.

Fluoride exposure status was examined in two ways. First, fluoride exposure status in the year of birth for a child was assessed in terms of the percentage of persons in a child's county and year of birth receiving fluoridated water (0% to 100%). Second, total fluoride exposure for a child was determined by adding together each child's values for the yearly percentage of persons receiving water from the fluoridated water supply in their county of residence over the child's 10 year period of enrollment. The resulting calculated values were utilized to compare a subcohort of children living in specific counties throughout their entire enrollment period where > 95% of the population was served by community water supplies with fluoridated water (fluoride-exposed) to a subcohort of children living in counties throughout their entire enrollment period where 0% of the population was served by community water supplies with fluoridated water (fluoride-unexposed).

Outcomes

The Florida Medicaid Claims file was examined to identify the date of service for the first claim in chronological order for each specific diagnosis examined. This date was assumed to be the date of onset for the outcome. The presence of TD (yes/no) was defined as any child with a claim specifying a diagnosis of dental carries (ICD-9 code: 521.xx). The presence of each of the following NDs (yes/no) was defined as any child with a claim specifying a diagnosis of autism spectrum disorder (ASD) (ICD-9 codes: 299.00 and/or 299.80), attention deficit-hyperactivity disorder (ADHD) (ICD-9 code: 314.01), intellectual disability (ID) (ICD-9 codes: 317 and/or 318.xx and/or 319), or specific delays in development (SDD) (ICD-9 codes: 315.xx). Children could receive one or more of the aforementioned diagnoses.

Statistical analyses

In statistical analyses, SAS statistics were utilized; a two-sided p-value < 0.05 was considered statistically significant; and power estimates were > 80%. The null hypothesis was that there would be no difference in the incidence rate of outcomes, regardless of fluoride exposure.

In the first set of statistical analyses, logistic regression modeling was utilized to examine the relationship between fluoride exposure in the year and county of birth for each child (continuous variable: 0% to 100%) and the diagnosis status (categorical variable: yes/no) for each outcome examined. Logistic regression modeling was also utilized to evaluate the relationship between fluoride exposure status in the fluoride-exposed and fluoride-unexposed (categorical variable: yes/no) subcohorts and diagnosis status (categorical variable: yes/no) for each outcome examined. Models were generated without adjustment for covariates (model I – odds ratio (OR)) and with adjustment for covariates (model II – adjusted odds ratio (aOR)). The covariates included in the adjusted model were the categorical variables of gender (male or female), race (Black, White, Asian, or Hispanic), malnutrition (ICD-9 codes: 263.0x, yes or no), disturbances of tooth eruption (ICD-9 code: 520.6, yes or no), lead toxicity (ICD-9 codes: 984.xx, yes or no), noxious influences affecting fetus or newborn via placenta or breast milk (ICD-9 codes: 760.7x, yes or no), and the continuous variables of date of birth and county of residence (county numeric codes: 1 to 67).

In the second set of statistical analyses, frequency modeling utilizing Fisher's exact test statistic was used to further evaluate outcomes significantly associated with fluoride exposure from unadjusted logistic regression modeling. The incidence rates of diagnosed outcomes in the fluoride-exposed subcohort as compared to the fluoride-unexposed subcohort were utilized to determine risk ratios and the attributable rate per 100 children. In addition, an analysis was undertaken to evaluate the impact of racial distribution differences between the fluoride-exposed and fluoride-unexposed subcohorts based on the results observed. An examination of the different racial groups (Asian, Black, Hispanic, and White) by fluoride exposure status revealed that > 90% of all Black, Hispanic, and Asian children were in the fluoride-exposed subcohort, whereas among White children, similar numbers of children were in both the fluoride-exposed (62%) and fluoride-unexposed (38%) subcohorts. As a result to help improve statistical power, subcohort analyses were undertaken on White children and non-White children (combined Asian, Black, and Hispanic) children.

Results

Table 1 summarizes the demographic characteristics of the children examined. Among all the cohorts examined, there were similarities in the gender distribution (about equal numbers of males and females) and mean

Table 1 Demographic characteristics of the children examined in this study[a]

Parameter Examined	Overall Cohort ($n=73,254$)	First 10 Years of Life Fluoride-Exposed Subcohort[b] ($n=25,662$)	First 10 Years of Life Fluoride-Unexposed Subcohort[c] ($n=2,509$)
Gender			
Male	36,634 (50.01%)	12,984 (50.60%)	1,193 (47.55%)
Female	36,620 (49.99%)	12,678 (49.40%)	1,316 (52.45%)
Date of Birth (yr)			
mean ± std (range)	1997 ± 3.32 (1990–2002)	1997 ± 3.30 (1990–2002)	1997 ± 3.36 (1990–2002)
Race[d]			
White	20,409 (27.86%)	2,465 (9.61%)	1,481 (59.03%)
Black	32,647 (44.57%)	10,809 (42.12%)	831 (33.12%)
Hispanic	19,869 (27.12%)	12,263 (47.79%)	196 (7.81%)
Asian	329 (0.45%)	125 (0.49%)	1 (0.04%)
Residency[e]			
District 1	4,040 (5.52%)	0 (0%)	264 (10.52%)
District 2	4,926 (6.72%)	38 (0.15%)	527 (21.01%)
District 3	8,160 (11.14%)	0 (0%)	1,119 (44.60%)
District 4	5,617 (7.67%)	2,781 (10.84%)	138 (5.50%)
District 5	4,241 (5.79%)	0 (0%)	0 (0%)
District 6	8,615 (11.76%)	370 (1.44%)	0 (0%)
District 7	5,360 (7.32%)	99 (0.39%)	0 (0%)
District 8	3,355 (4.58%)	0 (0%)	277 (11.04%)
District 9	6,608 (9.02%)	42 (0.16%)	184 (7.33%)
District 10	4,222 (5.76%)	4,222 (16.45%)	0 (0%)
District 11	18,110 (24.72%)	18,110 (70.57%)	0 (0%)
Health/Socioeconomic Status (Incidence rate per 100 children)			
Malnutrition	321 (0.44)	127 (0.49)[g]	4 (0.16)
Disturbances in Tooth Eruption	251 (0.34)	89 (0.35)	7 (0.28)
Lead Toxicity	5,875 (8.02)	1,197 (4.66)[g]	420 (16.74)
Noxious Influences Affecting Fetus/Infant via Placenta or Breast Milk	1,752 (2.39)	714 (2.78)[g]	22 (0.88)
Fluoridated Water Exposure (%)			
mean ± std (range)	65.87 ± 34.01 (0 to 100)[f]	97.62 ± 1.66 (95 to 100)	0

ICD-9 International Code of Disease, 9th revision, *std* standard deviation

[a] All children were enrolled from their date of birth for 120 consecutive months. All children had ≥ 10 outpatient office visits

[b] These children lived for 10 years within counties where > 95% of persons received fluoridated water supply

[c] These children lived for 10 years within counties where 0% of persons received fluoridated water supply

[d] All children examined were racially identified as White, Hispanic, Asian or Black

[e] All children were specified to have the same county of residence from birth to 10 years-old. There are a total of 67 counties in the state of Florida, which are grouped by the state of Florida based upon geographical areas into 11 districts

[f] Percent of persons for child's year and county of birth receiving fluoridated water exposure

[g] There were significant differences in the incidence rates between the first 10 year of life fluoride-exposed and fluoride-unexposed subcohorts

date of birth (1997). The racial distribution revealed differences between the cohorts examined. In the overall cohort, Black children (44.57%) were the highest percentage racial group. In the subcohorts examined, White children (59.03%) were the highest percentage racial group in the fluoride-unexposed subcohort and Hispanic children (47.79%) were the highest percentage racial group in the fluoride-exposed subcohort. In all cohorts examined, Asians were the smallest percentage racial group (< 1.0%). Among the various health/socioeconomic status covariates examined, the incidence rate per 100 children of lead toxicity (4.66 vs 16.74), malnutrition (0.49 vs 0.16), and noxious influences affecting the fetus/infant via the placenta or breast milk (2.78 vs 0.88) were significantly different when comparing the fluoride-exposed and fluoride-unexposed

subcohorts. On average, ~ 66% of persons in the year and county of birth for children in the overall cohort were fluoride-exposed.

Table 2 reveals the demographic characteristics of children diagnosed with the outcomes examined. The gender distribution for all the outcomes showed a male preponderance with the greatest male to female ratio observed for ASD (2.94) and the least for TD (1.15). The racial distribution showed TD (38.12%), ASD (37.09%), and ADHD (39.83%) were most commonly diagnosed among White children, whereas ID (45.05%) and SDD (44.17%) were most commonly diagnosed among Black children. The mean age of initial diagnoses ranged from the youngest for SDD at 4.15 years-old to the oldest for ADHD at 6.58 years-old. Among the NDs examined, the incidence rate per 100 children was highest for SDD (27.04) and ADHD (19.69) and lowest for ASD (0.96).

Table 3 shows the results of logistic regression modeling for the risks of the various outcomes examined as compared to water fluoride exposure in the year of birth and when comparing the fluoride-exposed and fluoride-unexposed subcohorts during the first 10 years of life. Overall, the dose-dependent effects of fluoride exposure in the year of birth were smaller than those observed when comparing the subcohorts of fluoride-exposed to fluoride-unexposed children.

Fluoridated water exposure in the year of birth revealed a dose-dependent statistically significant slight decrease in the risk of TD with increasing water fluoride exposure (OR = 0.996, aOR = 0.994). A dose-dependent statistically significant slight increase in the risk of ASD (OR = 1.006, aOR = 1.005) and ID (OR = 1.003, aOR = 1.006) was observed with increasing water fluoride exposure. Dose-dependent significant slight increases in ADHD (aOR = 1.001) and SDD (aOR = 1.002) risks were observed with increasing water fluoride exposure only in the adjusted model. When comparing the fluoride-exposed subcohort to fluoride-unexposed subcohort, significant increased risks for ASD (OR = 6.317, aOR = 5.575), ID (OR = 2.030, aOR = 3.868), and SDD (OR = 1.319, aOR = 1.505) were observed, while a significant decrease risk for TD (OR = 0.263, aOR = 0.345) was also observed.

Table 4 reveals the results of frequency modeling for the incidence rate of specific outcomes in the fluoride-exposed and fluoride-unexposed subcohorts. The incidence rate of TD was significantly ~ 3.6-fold lower in exposed as compared to unexposed children. The resultant attributable risk revealed an additional ~ 6 per 100 children diagnosed with TD. For the NDs examined, the incidences rate for ASD (risk ratio = 6.26), ID (risk ratio = 2.02), and SDD (risk ratio = 1.24) diagnoses were

Table 2 Demographic characteristics of the children diagnosed with the outcomes examined in this study[a]

Outcome	Gender Male Female	Race White Black Hispanic Asian	Age of Initial Diagnosis (yr) mean ± std (range)	Date of Birth (yr) mean ± std (range)	Incidence rate per 100 children (95% CI)
TD (*n* = 2,529)	1,350 (53.38%) 1,179 (46.62%)	964 (38.12%) 940 (37.17%) 610 (24.12%) 15 (0.59%)	6.06 ± 2.11 (0.89 to 10)	2000 ± 2.19 (1990 to 2002)	3.45 (3.32 to 3.59)
ASD (*n* = 701)	523 (74.61%) 178 (25.39%)	260 (37.09%) 214 (30.53%) 222 (31.67%) 5 (0.71%)	6.13 ± 2.26 (0.25 to 10)	1998 ± 3.40 (1990 to 2002)	0.96 (0.89 to 1.03)
ADHD (*n* = 14,425)	9,776 (67.77%) 4,649 (32.23%)	5,746 (39.83%) 5,470 (37.92%) 3,181 (22.05%) 28 (0.19%)	6.58 ± 1.88 (0.13 to 10)	1997 ± 3.25 (1990 to 2002)	19.69 (19.37 to 20.02)
ID (*n* = 717)	412 (57.46%) 305 (42.54%)	225 (31.38%) 323 (45.05%) 160 (22.32%) 9 (1.26%)	6.06 ± 2.50 (0.25 to 10)	1996 ± 3.33 (1990 to 2002)	0.98 (0.91 to 1.05)
SDD (*n* = 19,811)	12,103 (61.09%) 7,708 (38.91%)	6,291 (31.76%) 8,750 (44.17%) 4,689 (23.67%)	4.15 ± 2.80 (0.01 to 10)	1997 ± 3.21 (1990 to 2002)	27.04 (26.67 to 27.42)

ADHD attention deficit-hyperactivity disorder, *ASD* autism spectrum disorder, *CI* confidence interval, *ID* intellectual disability, *SDD* specific delays in development, *std* standard deviation, *TD* tooth decay

[a] All children were enrolled from their date of birth for 120 consecutive months. All children had ≥ 10 outpatient office visits

Table 3 Logistic regression modeling examining outcomes among children[a] as compared to fluoridated water exposure

Outcome	Model	Variable	Odds Ratio (95% CI)	χ^2	*p*-value
TD					
	I[b]	***Fluoridated Water Exposure in the Year of Birth[d]***	***0.996 (0.995 to 0.997)***	***56***	***< 0.0001***
		First 10 Years of Life Fluoridated Water Exposure (yes vs no)[e]	***0.263 (0.222 to 0.310)***	***249***	***< 0.0001***
	II[c]	***Fluoridated Water Exposure in the Year of Birth***	***0.994 (0.993 to 0.995)***	***77***	***< 0.0001***
		First 10 Years of Life Fluoridated Water Exposure (yes vs no)	***0.345 (0.267 to 0.447)***	***65***	***< 0.0001***
ASD					
	I	***Fluoridated Water Exposure in the Year of Birth***	***1.006 (1.003 to 1.008)***	***22***	***< 0.0001***
		First 10 Years of Life Fluoridated Water Exposure (yes vs no)	***6.317 (2.610 to 15.3)***	***17***	***< 0.0001***
	II	***Fluoridated Water Exposure in the Year of Birth***	***1.005 (1.002 to 1.008)***	***10***	***< 0.005***
		First 10 Years of Life Fluoridated Water Exposure (yes vs no)	***5.575 (2.104 to 14.8)***	***12***	***< 0.001***
ADHD					
	I	***Fluoridated Water Exposure in the Year of Birth***	0.999 (0.999 to 1.000)		NS
		First 10 Years of Life Fluoridated Water Exposure (yes vs no)	***0.845 (0.765 to 0.934)***	***11***	***< 0.0001***
	II	***Fluoridated Water Exposure in the Year of Birth***	***1.001 (1.000 to 1.002)***	***10***	***< 0.005***
		First 10 Years of Life Fluoridated Water Exposure (yes vs no)	1.092 (0.944 to 1.263)		NS
ID					
	I	***Fluoridated Water Exposure in the Year of Birth***	***1.003 (1.000 to 1.005)***	***5.05***	***< 0.05***
		First 10 Years of Life Fluoridated Water Exposure (yes vs no)	***2.030 (1.136 to 3.629)***	***5.71***	***< 0.05***
	II	***Fluoridated Water Exposure in the Year of Birth***	***1.006 (1.003 to 1.009)***	***16***	***< 0.0001***
		First 10 Years of Life Fluoridated Water Exposure (yes vs no)	***3.868 (1.752 to 8.542)***	***11***	***< 0.001***
SDD					
	I	***Fluoridated Water Exposure in the Year of Birth***	1.000 (1.000 to 1.001)		NS
		First 10 Years of Life Fluoridated Water Exposure (yes vs no)	***1.319 (1.192 to 1.458)***	***29***	***< 0.0001***
	II	***Fluoridated Water Exposure in the Year of Birth***	***1.002 (1.001 to 1.003)***	***39***	***< 0.0001***
		First 10 Years of Life Fluoridated Water Exposure (yes vs no)	***1.505 (1.308 to 1.733)***	***33***	***< 0.0001***

Bold-Italicized results are statistically significant

ADHD attention deficit-hyperactivity disorder, *ASD* autism spectrum disorder, *CI* confidence interval, *ID* intellectual disability, *NS* not statistically significant, *SDD* specific delays in development, *TD* tooth decay

[a] All children examined in this study were enrolled from their date of birth for 120 consecutive months. All children had ≥ 10 outpatient office visits and lived in the same county of residence during the study periods

[b] This model was unadjusted for any covariates

[c] This model was adjusted for the covariates of gender, date of birth, race, malnutrition status, maternal noxious influences affecting fetus or newborn via placenta or breast milk, disturbances in tooth eruption, lead intoxication, and county of residency

[d] This was determined by the percent of persons exposed to fluoridated water in each child's year and county of birth

[e] Yes = Children lived for 10 years in counties where > 95% of persons received fluoridated water. No = These children lived for 10 years in counties where 0% of persons received fluoridated water

all significantly increased among exposed as compared to unexposed children. The resultant attributable risks per 100 children were 1.05 for ASD, 0.49 for ID, and 4.90 for SDD. In addition, Table 4 shows the results of a further analysis that was undertaken for White children and non-White children. The results observed were generally consistent with the aforementioned findings among children of all racial groups.

Discussion

The results of this multi-decade, large population-based, hypothesis-testing longitudinal cohort study provide important new insights regarding the safety and effectiveness of water fluoridation. Dose-dependent increases in fluoride exposure in the year of birth were associated with significant slight reductions in the incidence rate of TD, while also being associated with significant slight increases in the incidence rate of NDs. The observed associations remained significant and, were of larger magnitude, than those observed for fluoride exposure in the year of birth, when comparing children fluoride-exposed to fluoride-unexposed during the first 10 years of life. Finally, the phenomena were significant when utilizing different statistical modeling techniques and when adjusting/stratifying the models for numerous covariates.

Table 4 Frequency modeling results to evaluate outcomes examined among children[a] with fluoridated water exposure[b] as compared to children without fluoridated water exposure[c]

Race	Outcome	Incidence Rate per 100 Children First 10 Years of Life Fluoride-Exposed[b]	Incidence Rate per 100 Children First 10 Years of Life Fluoride-Unexposed[c]	Risk Ratio (95% CI) Attributable Rate per 100 Children *p*-value
All[d]		**Total *n* = 25,662**	**Total *n* = 2,509**	
	TD	2.24 (*n* = 574)	8.01 (*n* = 201)	***0.28 (0.322 to 0.701)***
				-5.77 (-6.85 to -4.70)
				< 0.0001
	ASD	1.25 (*n* = 320)	0.20 (*n* = 5)	***6.26 (2.59 to 15.1)***
				1.05 (0.83 to 1.27)
				< 0.0001
	ID	0.97 (*n* = 248)	0.48 (*n* = 12)	***2.02 (1.13 to 3.60)***
				0.49 (0.19 to 0.78)
				< 0.05
	SDD	25.6 (*n* = 6,567)	20.7 (*n* = 519)	***1.24 (1.14 to 1.34)***
				4.90 (3.23 to 6.58)
				< 0.0001
White		***n* = 2,465**	**Total *n* = 1,481**	
	TD	3.57 (*n* = 88)	8.51 (*n* = 126)	***0.42 (0.322 to 0.701)***
				-4.94 (-6.54 to -3.34)
				< 0.0001
	ASD	2.19 (*n* = 54)	0.20 (*n* = 3)	***10.8 (3.39 to 34.5)***
				1.99 (1.37 to 2.61)
				< 0.0001
	ID	1.26 (*n* = 31)	0.34 (*n* = 5)	***3.73 (1.45 to 9.56)***
				0.92 (0.39 to 1.45)
				< 0.005
	SDD	33 (*n* = 813)	21.9 (*n* = 324)	***1.51 (1.35 to 1.69)***
				11.1 (8.30 to 13.9)
				< 0.0001
non-White		***n* = 23,197**	**Total *n* = 1,028**	
	TD	2.10 (*n* = 486)	7.30 (*n* = 75)	***0.29 (0.23 to 0.36)***
				-5.20 (-6.80 to -3.6)
				< 0.0001
	ASD	1.15 (*n* = 266)	0.19 (*n* = 2)	***5.89 (1.47 to 23.7)***
				0.95 (0.65 to 1.25)
				< 0.01
	ID	0.94 (*n* = 217)	0.68 (*n* = 7)	***1.37 (0.65 to 2.91)***
				0.25 (-0.26 to 0.77)
				NS
	SDD	24.8 (*n* = 5,754)	19 (*n* = 195)	***1.31 (1.15 to 1.49)***
				5.84 (3.38 to 8.30)
				< 0.0001

The Fischer's exact test statistic was utilized

Bold-Italicized results are statistically significant

ASD autism spectrum disorder, *CI* confidence interval, *ID* intellectual disability, *NS* not statistically significant, *SDD* specific delays in development, *TD* tooth decay

[a] All children examined in this study were enrolled from their date of birth for 120 consecutive months. All children had ≥ 10 outpatient office visits

[b] These children lived for 10 years within counties where > 95% of persons received fluoridated water

[c] These children lived for 10 years within counties where 0% of persons received fluoridated water

[d] Separation of the data by racial cohorts was possible only for White children and non-White children because among Black (93%), Hispanic (98%), and Asian (99%) most children were fluoride-exposed as compared to fluoride-unexposed (the combination of all non-White children was designed to improve statistical power)

The methods utilized and results observed in the present study particularly overlap with a previous epidemiological study undertaken by investigators from the US CDC and the state of Louisiana [12]. The investigators examined Louisiana Medicaid dental reimbursements and eligibility from July 1995 through June 1996 for children and water fluoridation status as the percentage of the population in the child's community of residence receiving fluoridated water. Overall, statistical modeling revealed that children living in communities without fluoridated water as compared to those living in communities with fluoridated water were significantly about threefold more likely to receive TD-related services. This result is consistent with the observation from this study that children fluoride-exposed as compared to fluoride-unexposed were significantly, about three-fold more likely, to be diagnosed with TD. This consistency in results, across the two studies, provides important support for the validity of the epidemiological methods utilized in both studies. Unfortunately, the Louisiana Medicaid study investigators undertook no safety assessments.

As to safety, there are recent epidemiological studies in Canada, Mexico, and the US revealing significant associations between higher prenatal fluoride exposure with poor neurocognitive outcomes [13–18] and a recent meta-analysis identifying that fluoride exposure (based upon drinking water and urinary fluoride concentrations) were associated overall with significant reductions in IQ scores in a dose-dependently manner [19]. While the results observed in this study are consistent with previous observations, the present study is differentiated from these previous studies in several key aspects, including: (1) examination of a longitudinal cohort of children prospectively enrolled in a healthcare system from birth until 10 years-old with known water fluoride exposure statuses over their entire enrollment period; (2) outcomes based upon standardized ICD-9 coding diagnoses made by healthcare providers as part of their routine patient care; and (3) the large and diverse sample of study subjects examined.

The results observed in this study are biologically plausible [4, 5, 20, 21]. A recent review described fluoride prevents TD by interfering with the processes of mineral exchanges (demineralization, remineralization) to which teeth frequently are subjected to by biofilms and a diet rich in fermentable sugars [20]. Another recent review reported that fluoride-associated neurotoxicity is associated with increased oxidative stress, synaptic and neurotransmission dysfunction, disruption of mitochondrial/energy metabolism, and calcium channel dysregulation [21].

Another important consideration regarding the observed results in this study is the type and dose of fluoride exposure. The US CDC describes that fluorosilicic acid (H_2SiF_6), a halogenated inorganic acid, is the water fluoridation compound most widely used in US community water systems [22]. It rapidly yields free fluoride when mixed with water. The US CDC supports water fluoridation at a recommended level of 0.7 mg of fluoride per liter of water [22]. Significant correlations between household water fluoride and plasma fluoride concentrations were observed among US children [23]. Estimated average dietary intake (including water) of fluoride for children living in areas with fluoridated water is between 0.03 to 0.06 mg/kilogram/day [24] and water and processed beverages comprise about 75% of a person's daily fluoride intake [25].

In order to further quantify water fluoride exposure in the state of Florida, independent of added water fluoride in community water systems, an assessment of fluoride concentrations in untreated groundwater fluoride samples collected from 1998–2017 by the US Geological Survey (USGS) was conducted [26]. The USGS examined 38,105 groundwater samples from across the US. A total of 727 samples (1.91% of the total) were collected from the state of Florida. The data revealed the median milligrams of fluoride per liter of water was 0.2 (interquartile range = 0 to 0.3, min = 0, and max = 3.3). Thus, in the state of Florida, exposure to fluoridated community water supplies resulted in exposure to significantly higher water fluoride concentrations than those occurring from natural sources.

Previous studies demonstrated dose-dependent and timing-related relationships between water fluoride exposure and a wide-range of effects [3–5]. The current study shows both of these phenomena. Variations in water fluoride exposure in the year of birth is associated with dose-dependent slight, statistically significant long-term associations with TD and ND outcomes. By increasing the duration and magnitude of water fluoride exposure/lack of exposure over the first 10 years of life, the results reveal fluoride exposure is associated with larger significant associations with TD and ND outcomes than those observed when only examining variations in water fluoride status in the year of birth.

Strengths and limitations

The epidemiological methods employed are an important strength of this study. Two separate techniques to estimate fluoride exposure status for each study subject were utilized, and, thus, determine a dose-dependent and absolute risk for each of the outcomes examined. In addition, it is known that confounders/biases changes in diagnosis ascertainment over time, racial/ethnic disparities,

and socioeconomic status may influence study results [27–30]. As such, the covariates of date of birth, gender, race, maternal health status, environmental toxicant exposure, socioeconomic factors, and disturbances in tooth eruption were employed in adjusted statistical models, and analyses were undertaken to compare the effects of fluoride when comparing children of the same racial group. All told, consistent and significant associations between fluoride exposure and the outcomes examined were generally observed in each analysis. In addition, the biological plausibility of the results, consistency with previous studies, and opposite associations between fluoride exposure and measures of safety and effectiveness, support the validity of epidemiological methods employed.

Another important strength of this study is the large and diverse population examined over > 2 decades. The children were from a wide-range of ethnicities and geographical locations. All children examined were continuously enrolled from birth until 10 years-old and actively utilized healthcare services from Florida Medicaid. Healthcare providers determined the diagnostic status of each child on a prospective basis as part of routinely provided healthcare services and without knowledge of fluoride exposure status. Exposure status was independently determined in this study by examination of detailed data accumulated by the PHDP. As such, potential biases/confounders, such as factors influencing study enrollment or diagnostic status based upon known exposures, were minimized by the study design.

A potential limitation of this study is that no direct, individualized measure of fluoridated water exposure was examined. As a result, there may be differences in individualized liquid consumption patterns from different sources of water (e.g., drinking bottled water without fluoride, drinking community water supplies, or drinking prepackaged products such as juices, sodas, etc.) and also the quantity of water ingested (e.g., drinking a little vs a lot of water). These types of individualized fluoride measures are difficult to obtain for large populations, and were not the primary measure of exposure utilized in many previous studies. It is believed that such potential differences in fluoride exposure would occur with equal probabilities among all the children, and thus, should not bias/confound the results observed. Further, given that lower income families comprise a significant portion of Florida Medicaid enrollees, it is unlikely that significant consumption of water from alternative sources would have occurred with greater frequency or differential frequency, due to expense, among the children examined, so as to bias/confound the results observed. Future studies should evaluate the impact of differences in individualized liquid consumption patterns.

Another potential limitation of this study is that diagnostic status was determined by diagnoses (presence/absence) made on claims submitted by healthcare providers to Florida Medicaid for reimbursement of services provided. As such, for each outcome, no independent diagnostic verification, determination of severity, or long-term adverse effects were possible to determine. In addition, outcomes examined had to be sufficiently impactful, so as to require examination and diagnosis by a healthcare provider.

Despite these limitations, previous studies of IHRD data revealed diagnostic outcome sensitivity/specificity consistent with those observed in other studies [6–10]. Furthermore, the incidence rates and timing of ND diagnoses in this study are consistent with previous studies [31]. Finally, the incidence rate of TD diagnoses in this study are consistent with previous studies measuring the incidence rate of treated TD (i.e., a significant percentage of examined children do not receive treatment for TD) [32]. Future studies should evaluate the impact differences in diagnostic status in other databases.

An additional potential limitation of this study is that there is a significant body of evidence supporting the multifactorial etiology of NDs [33]. Many different environmental exposures and genetic disorders may be risk factors for NDs, and they, in turn, may be influenced by differential genetic susceptibilities, epigenetic mechanisms, and effect modifiers. Thus, the associations between water fluoride exposure and the risk for NDs observed in this study must be viewed in this multifaceted context.

A final consideration regarding the observed statistical associations is that they must be considered within the context of the nine principles used to determine if an environmental exposure causes an outcome under the Bradford Hill criteria [34]. As such, while the present study provides important epidemiological evidence to meet some of the Bradford Hill criteria, it must be integrated and interpreted in the wider context of many other studies examining water fluoride safety and effectiveness.

Conclusions

This cohort study revealed dose-dependent and overall significant associations between increasing fluoride exposure and reduced TD and between increasing fluoride exposure and increasing rates of NDs. Given the beneficial and harmful findings from this study, new risk/benefit analyses should be undertaken regarding water fluoridation programs. Finally, it is recommended that future studies by undertaken on large populations in other databases.

Abbreviations

aOR	Adjusted Odds ratio
ADHD	Attention Deficit-Hyperactivity Disorder
ASD	Autism spectrum disorder
CDC	Centers for Disease Control and Prevention
IHRD	Independent Healthcare Research Database
IQ	Intelligence Quotient
ICD-9	International Code for Disease, 9th revision
ID	Intellectual Disability
NDs	Neurodevelopmental Disorders
SDD	Specific Delays in Development
OR	Odds Ratio
TD	Tooth Decay
US	United States
USGS	United States Geological Survey

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None.

Authors' contributions
DAG conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted. MRG conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. All authors read and approved the final manuscript.

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Data availability
Florida Medicaid data is publicly available upon request to the Public Records Coordination Office of the Florida Agency for Health Care Administration (email: publicrecordsreq@ahca.myflorida.com, phone: (850)412–3688). The final dataset utilized in this study is available upon request to Dr. Mark R. Geier.

Declarations

Ethics approval and consent to participate
The data in the IHRD were assembled and accessed under approval by the Liberty Institutional Review Board (IRB) (Deland, FL). The Liberty IRB approved this research as not involving human subject research, and thus, informed consent was not needed.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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