Supplementary material

Fluoride analysis

All measured urine samples from the OCC cohort had fluoride concentrations higher than the limit of determination (0.02 mg/L), i.e., the lowest point on the calibration curve (CV% < 3%). Method validation over six different days showed an average imprecision of the method less than 5.1%. The accuracy of the method was controlled prior to analysis of each batch of samples by analyzing the fluoride reference solution CRM at 0.52 + 0.02 mg/L (Merck, Darmstadt, Germany). The mean concentration of all series was 0.54 mg/mL (tolerance range: 0.48 – 0.56 mg/L). All batches of urine samples analyzed contained quality control samples from The German Quality Assessment Scheme (G-EQUAS), (control material 2A/B). The mean accuracy ranged from 95.0 to 104.7% and all measurements were well within the tolerance range. The U-F concentrations were not related to season.

Table S1 Estimated regression coefficients (β, with standard error, SE) for the creatinine-adjusted fluoride concentration (mg/L) in the two subgroups of mothers who delivered a urine sample, with *p* values for difference between the two groups determined by Z-test. The simple model is adjusted for parental education and preterm birth. The comprehensive model accounts also for age at the time of testiing, breastfeeding duration, examiner, school grade, school type and smoking and alcohol habits of the mother during pregnancy.

	24h sample (mg/L)		spot sample (mg/L)		
	β	SE	*β*	SE	*p* value
Simple model					
All	0.36	1.06	-0.05	0.76	0.35
Girl	0.67	1.54	-0.83	1.10	0.13
Boy	0.09	1.45	0.69	1.06	0.39
Comprehensive model					
All	-0.72	1.28	0.58	1.07	0.14
Girl	-0.91	1.71	-0.78	1.45	0.29
Boy	-0.50	1.84	2.14	1.55	0.08

Table S2 Regression coefficients adjusted for covariables for a linear change in the FSIQ outcome for boys and girls combined, at an increase by 1 mg/L in creatinine-adjusted maternal U-F concentration in the present (OCC) study, the MIREC study, and the ELEMENT study, and jointly for all three.

	OCC		MIREC		ELEMENT		Joint		
Parameter	β	*p*	β	*p*	β	*p*	β	*p*	p_{diff}
Result	-0.94	0.43	-2.01	0.16	-4.09	0.009	-2.06	0.009	0.28

Table S3. BMC values for creatinine-adjusted maternal U-F (mg/L) for three models and for both sexes of the three studies and the combined data, where the outcome in the ELEMENT study is the McCarthy GCI score. The fit of the regression models was compared by the AIC (where lower values indicate a better fit).

		OCC (n= 837)		MIREC (n=407)		ELEMENT GCI (n=355)		All three studies (n=1,599)		
	Sex	BMC	BMCL	BMC	BMCL	BMC	BMCL	BMC	BMCL	AIC
Linear	All	0.920	0.303	0.497	0.228	0.245	0.142	0.474	0.284	12552
	Girls	0.487	0.189	∞	0.609	0.182	0.106	0.633	0.280	12550
	Boys	3.609	0.309	0.201	0.125	0.426	0.149	0.393	0.225	12550
Piecewise models										
Breakpoint 0.5	All	2.102	0.987	1.751	0.092	0.054	0.024	1.491	0.418	12552
	Girls	1.764	0.764	∞	0.309	0.081	0.025	2.197	0.935	12553
	Boys	2.986	0.205	0.086	0.040	0.030	0.013	0.479	0.097	12553
Breakpoint 0.75	All	1.500	0.795	0.166	0.081	0.094	0.049	0.984	0.231	12551
	Girls	1.299	0.516	∞	0.125	0.112	0.046	1.448	0.303	12552
	Boys	2.028	0.268	0.082	0.049	0.072	0.034	0.268	0.120	11552

Abbreviations: AIC, Akaike Information Criterion; BMC, benchmark concentration; BMCL, benchmark concentration level; GCI, McCarthy Scale General Cognitive Index; OCC, Odense Child Cohort.

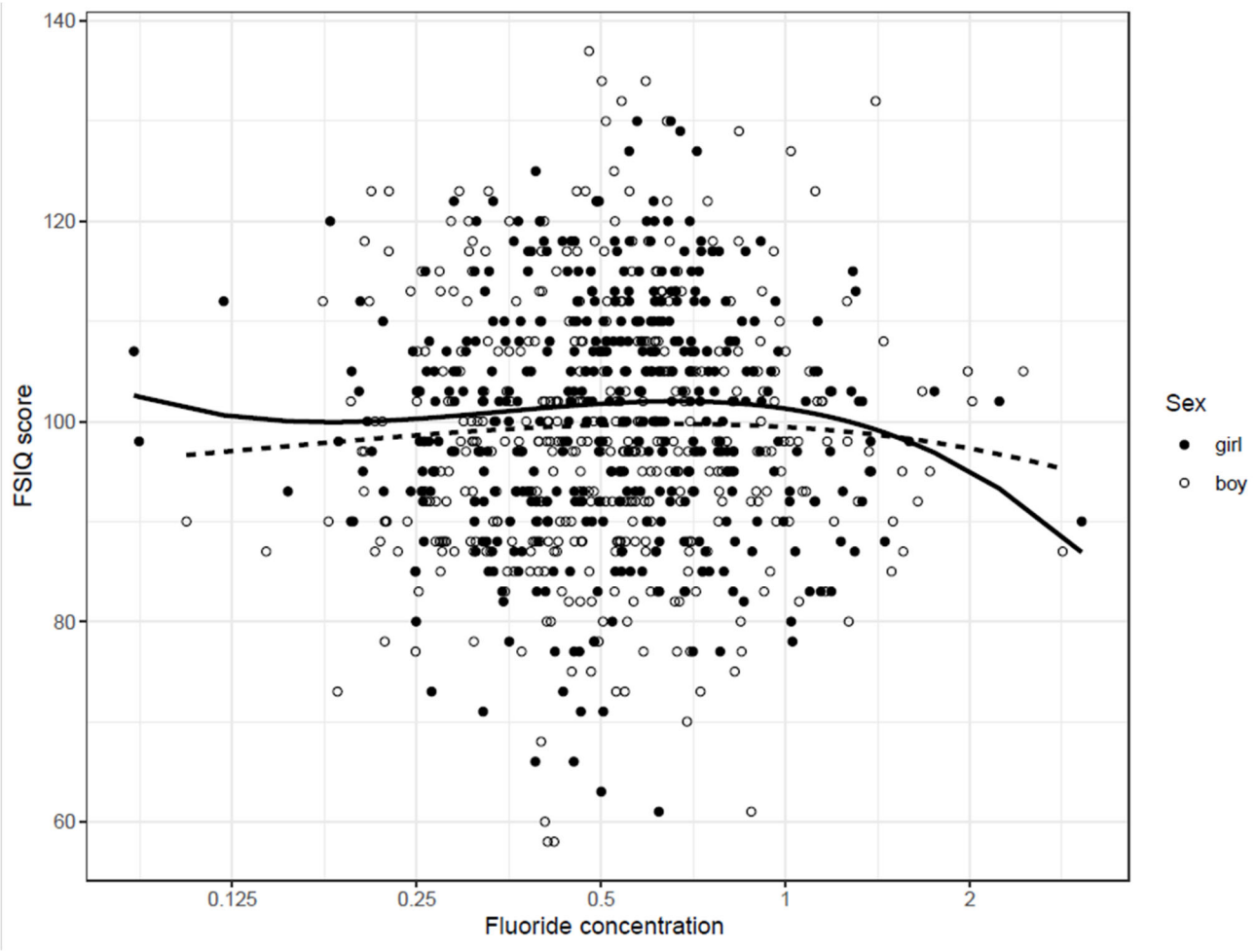

Figure S1 Cubic spline model of the creatinine-adjusted maternal U-F concentration during pregnancy (log-transformed) as a predictor of Full-Scale IQ (FSIQ) in OCC children at age 7, with interaction by sex and type of urine sample as a fixed effect. The model is also adjusted for parental education and preterm birth The filled circles and the full regression line are for girls, and the open circles and the dotted line refer to the boys.