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Supplemental Material

Fluoride in Drinking Water, Diet, and Urine in Relation to Bone Mineral Density and Fracture Incidence in Postmenopausal Women

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Table S1.

Cross-sectional mean differences in BMD (β coefficients (95% CI), g/cm²) across tertiles of urinary fluoride (mg/g creatinine) and dietary fluoride (mg/d) with BMD at the lumbar spine and femoral neck among women with approximately constant drinking water fluoride concentrations from 1982 to baseline.

	Tertiles of urinary fluoride, n = 3,478				Tertiles of dietary fluoride, n = 3,387			
	1	2	3	<i>p</i> trend	1	2	3	<i>p</i> trend
Lumbar spine								
Age adjusted β (95% CI)	Ref.	-0.015 (-0.031 to 0.001)	-0.026 (-0.042 to -0.010)		Ref.	0.006 (-0.011 to 0.022)	0.022 (0.006 to 0.038)	
Multivariable adjusted β (95% CI)	Ref.	0.006 (-0.009 to 0.021)	0.010 (-0.005 to 0.025)	0.19	Ref.	0.005 (-0.010 to 0.020)	0.018 (0.003 to 0.033)	0.02
Femoral neck								
Age adjusted β (95% CI)	Ref.	-0.003 (-0.013 to 0.006)	-0.012 (-0.021 to -0.002)		Ref.	0.006 (-0.003 to 0.016)	0.012 (0.003 to 0.022)	
Multivariable adjusted β (95% CI)	Ref.	0.007 (-0.002 to 0.015)	0.008 (-0.001 to 0.017)	0.08	Ref.	0.006 (-0.003 to 0.015)	0.009 (0.000 to 0.018)	0.05

Multivariable-adjusted models were adjusted for age, education, height, total fat mass, lean body mass, parity, smoking status, physical activity, alcohol intake, diabetes, eGFR, tertiles of urinary excretion of calcium (for urinary fluoride) or tertiles of dietary intake of calcium (for dietary fluoride), use of calcium supplements, use of vitamin D supplements, ever use of estrogen and ever use of corticosteroids. Urinary fluoride models were additionally adjusted for serum Beta-CrossLaps (ng/L)

91 women were excluded from the dietary fluoride analyses because of missing dietary fluoride information either due to responding to a shorter version of the FFQ or having missing / inadequate reported dietary intake (energy intake outside 3 SD of log-transformed mean)

Abbreviations: β : Beta coefficient, BMD: bone mineral density (g/cm²), eGFR: estimated glomerular filtration rate, CI: confidence interval.

Table S2.

Hazard ratios of osteoporotic fractures, excluding vertebral fractures, and corresponding 95% confidence intervals by tertiles of urinary fluoride (mg/g creatinine) and dietary fluoride (mg/d).

	Tertiles of urinary fluoride				Tertiles of dietary fluoride			
	1	2	3	<i>p</i> trend	1	2	3	<i>p</i> trend
Cases	150	158	208		157	165	163	
Person years	13,465	13,816	13,668		12,794	13,124	13,136	
Age-adjusted HR (95 %CI)	Ref.	1.03 (0.83 – 1.29)	1.33 (1.08 – 1.64)		Ref.	1.07 (0.86 – 1.33)	1.13 (0.91 – 1.41)	
Multivariable-adjusted HR (95 %CI)	Ref.	1.02 (0.81 – 1.27)	1.24 (1.00 – 1.54)	0.04	Ref.	1.07 (0.86 – 1.34)	1.11 (0.89 – 1.39)	0.35

Multivariable-adjusted models were adjusted for age, education, height, total fat mass, lean body mass, parity, smoking status, physical activity, alcohol intake, diabetes, eGFR, tertiles of urinary excretion of calcium (for urinary fluoride) or tertiles of dietary intake of calcium (for dietary fluoride), use of calcium supplements, use of vitamin D supplements, ever use of estrogen and ever use of corticosteroids. Urinary fluoride models were additionally adjusted for serum Beta-CrossLaps (ng/L).

Abbreviations: HR: hazard ratio, CI: confidence interval, eGFR: estimated glomerular filtration rate

The total number of participants in the urinary fluoride and dietary fluoride analyses were 4,306 and 4,072, respectively. 234 women were excluded from the dietary fluoride analyses because of missing dietary fluoride information either due to responding to a shorter version of the FFQ or having missing / inadequate reported dietary intake (energy intake outside 3 SD of log-transformed mean)

For each outcome, women contributed with person time from the date of clinical examination until the of date of the specific event studied, death, or end of follow-up at December 31st, 2017.

Table S3.

Multivariable adjusted hazard ratios of total, osteoporotic and hip fractures and corresponding 95% confidence intervals by tertiles of urinary fluoride (mg/g creatinine) and dietary fluoride (mg/d), respectively. Multivariable models are further adjusted for baseline bone mineral density (BMD)

	Tertiles of urinary fluoride				Tertiles of dietary fluoride			
	1	2	3	<i>p</i> trend	1	2	3	<i>p</i> trend
All fractures								
Cases	261	267	322		268	272	259	
Person years	12,815	13,232	12,974		12,172	12,505	12,572	
Multivariable-adjusted HR (95 %CI)	1 (Ref)	0.97 (0.82 – 1.16)	1.15 (0.97 – 1.36)	0.08	1 (Ref)	1.03 (0.87 – 1.22)	1.03 (0.86 – 1.22)	0.80
Major osteoporotic fractures								
Cases	157	161	211		162	169	167	
Person years	13,465	13,817	13,638		12,794	13,124	13,136	
Multivariable-adjusted HR (95 %CI)	1 (Ref)	1.02 (0.81 – 1.27)	1.24 (1.00 – 1.53)	0.04	1 (Ref)	1.08 (0.87 – 1.34)	1.14 (0.91 – 1.42)	0.25
Hip fractures								
Cases	50	54	83		54	55	65	
Person years	14,127	14,477	14,416		13,464	13,801	13,804	
Multivariable-adjusted HR (95 %CI)	1 (Ref)	1.15 (0.77 – 1.70)	1.58 (1.09 – 2.28)	0.01	1 (Ref)	1.08 (0.73 – 1.58)	1.64 (1.13 – 2.37)	< 0.01

Multivariable-adjusted models were apart from baseline bone BMD adjusted for age, education, height, total fat mass, lean body mass, parity, smoking status, physical activity, alcohol intake, diabetes, eGFR, tertiles of urinary excretion of calcium (for urinary fluoride) or tertiles of dietary intake of calcium (for dietary fluoride), use of calcium supplements, use of vitamin D supplements, ever use of estrogen and ever use of corticosteroids. Urinary fluoride models were additionally adjusted for serum Beta-CrossLaps (ng/L).

Abbreviations: HR: hazard ratio, CI: confidence interval, eGFR: estimated glomerular filtration rate

The total number of participants in the urinary fluoride and dietary fluoride analyses were 4,306 and 4,072, respectively. 234 women were excluded from the dietary fluoride analyses because of missing dietary fluoride information either due to responding to a shorter version of the FFQ or having missing / inadequate reported dietary intake (energy intake outside 3 SD of log-transformed mean)

For each outcome, women contributed with person time from the date of clinical examination until the of date of the specific event studied, death, or end of follow-up at December 31st, 2017.

Table S4.

Cross-sectional mean differences in BMD (β coefficients (95% CI), g/cm²) across tertiles of urinary fluoride (mg/g creatinine) and dietary fluoride (mg/d) with BMD at the lumbar spine and femoral neck, among women of the Swedish Mammography Cohort – Clinical, including individuals excluded from main analysis because of missing bone mineral density data on either hip or spine.

	Tertiles of urinary fluoride				Tertiles of dietary fluoride			
	1	2	3	<i>p</i> trend	1	2	3	<i>p</i> trend
Lumbar spine, n = 4,445					Lumbar spine, n = 4,203			
Age adjusted β (95% CI)	Ref.	-0.015 (-0.029 to 0.000)	-0.022 (-0.036 to -0.008)		Ref.	0.000 (-0.015 to 0.014)	0.017 (0.003 to 0.032)	
Multivariable adjusted β (95% CI)	Ref.	0.006 (-0.007 to 0.019)	0.015 (0.002 to 0.028)	0.02	Ref.	0.004 (-0.010 to 0.017)	0.018 (0.005 to 0.032)	<0.01
Femoral neck, n = 4,307					Femoral neck, n = 4,073			
Age adjusted β (95% CI)	Ref.	-0.003 (-0.011 to 0.006)	-0.012 (-0.020 to -0.003)		Ref.	0.005 (-0.004 to 0.013)	0.009 (0.001 to 0.018)	
Multivariable adjusted β (95% CI)	Ref.	0.007 (-0.001 to 0.015)	0.009 (0.001 to 0.016)	0.04	Ref.	0.006 (-0.002 to 0.014)	0.008 (0.000 to 0.016)	0.06

Multivariable-adjusted models were adjusted for age, education, height, total fat mass, lean body mass, parity, smoking status, physical activity, alcohol intake, diabetes, eGFR, tertiles of urinary excretion of calcium (for urinary fluoride) or tertiles of dietary intake of calcium (for dietary fluoride), use of calcium supplements, use of vitamin D supplements, ever use of estrogen and ever use of corticosteroids. Urinary fluoride models were additionally adjusted for serum Beta-CrossLaps (ng/L)

242 women were excluded from the dietary fluoride analyses because of missing dietary fluoride information either due to responding to a shorter version of the FFQ or having missing / inadequate reported dietary intake (energy intake outside 3 SD of log-transformed mean)

Abbreviations: β : Beta coefficient, BMD: bone mineral density (g/cm²), eGFR: estimated glomerular filtration rate, CI: confidence interval.

Table S5.

Hazard ratios of total, osteoporotic and hip fractures and corresponding 95% confidence intervals by tertiles of urinary fluoride (mg/g creatinine) and dietary fluoride (mg/d), respectively, among women of the Swedish Mammography Cohort – Clinical, including individuals excluded from main analysis because of missing bone mineral density data on either hip or spine.

	Tertiles of urinary fluoride, n = 4,451				Tertiles of dietary fluoride, n = 4,209			
	1	2	3	<i>p</i> trend	1	2	3	<i>p</i> trend
All fractures								
Cases	272	281	335		276	290	269	
Person years	13,198	13,643	13,384		12,558	12,874	12,962	
Age-adjusted HR (95 %CI)	1 (Ref)	1.00 (0.84 – 1.18)	1.17 (1.00 – 1.38)		1 (Ref)	1.06 (0.90 – 1.26)	1.03 (0.87 – 1.22)	
Multivariable-adjusted HR (95 %CI)	1 (Ref)	0.99 (0.84 – 1.17)	1.13 (0.95 – 1.33)	0.12	1 (Ref)	1.07 (0.90 – 1.26)	1.01 (0.85 – 1.20)	0.97
Major osteoporotic fractures								
Cases	165	172	219		169	182	173	
Person years	13,860	14,247	14,075		13,176	13,523	13,555	
Age-adjusted HR (95 %CI)	1 (Ref)	1.02 (0.83 – 1.27)	1.26 (1.03 – 1.54)		1 (Ref)	1.10 (0.89 – 1.35)	1.10 (0.89 – 1.37)	
Multivariable-adjusted HR (95 %CI)	1 (Ref)	1.01 (0.81 – 1.25)	1.20 (0.97 – 1.47)	0.07	1 (Ref)	1.10 (0.89 – 1.36)	1.08 (0.87 – 1.34)	0.50
Hip fractures								
Cases	53	55	87		57	59	66	
Person years	14,551	14,961	14,862		13,864	14,248	14,248	
Age-adjusted HR (95 %CI)	1 (Ref)	1.03 (0.70 – 1.49)	1.45 (1.03 – 2.04)		1 (Ref)	1.12 (0.78 – 1.61)	1.47 (1.03 – 2.10)	
Multivariable-adjusted HR (95 %CI)	1 (Ref)	1.06 (0.72 – 1.56)	1.44 (1.01 – 2.06)	0.03	1 (Ref)	1.13 (0.79 – 1.64)	1.47 (1.02 – 2.10)	0.04

Multivariable-adjusted models were adjusted for age, education, height, total fat mass, lean body mass, parity, smoking status, physical activity, alcohol intake, diabetes, eGFR, tertiles of urinary excretion of calcium (for urinary fluoride) or tertiles of dietary intake of calcium (for dietary fluoride), use of calcium supplements, use of vitamin D supplements, ever use of estrogen and ever use of corticosteroids. Urinary fluoride models were additionally adjusted for serum Beta-CrossLaps (ng/L).

Abbreviations: HR: hazard ratio, CI: confidence interval, eGFR: estimated glomerular filtration rate

For each outcome, women contributed with person time from the date of clinical examination until the date of the specific event studied, death, or end of follow-up at December 31st, 2017. 242 women were excluded from the dietary fluoride analyses because of missing dietary fluoride information either due to responding to a shorter version of the FFQ or having missing / inadequate reported dietary intake (energy intake outside 3 SD of log-transformed mean)

Table S6.

Cross-sectional mean differences in Bone mineral density (BMD)(β coefficients (95% CI), g/cm²) across tertiles of urinary fluoride (mg/g creatinine) with BMD at the lumbar spine and femoral neck among women of the Swedish Mammography Cohort – Clinical with complete exposure data.

	Tertiles of urinary fluoride, n = 4,072			p trend
	1	2	3	
Lumbar spine				
Age adjusted β (95% CI)	Ref.	-0.014 (-0.029 to 0.001)	-0.021 (-0.036 to -0.006)	
Multivariable adjusted β (95% CI)	Ref.	0.006 (-0.007 to 0.020)	0.015 (-0.001 to 0.028)	0.03
Femoral neck				
Age adjusted β (95% CI)	Ref.	-0.003 (-0.013 to 0.005)	-0.011 (-0.020 to -0.003)	
Multivariable adjusted β (95% CI)	Ref.	0.007 (-0.001 – 0.015)	0.008 (0.000 – 0.016)	0.06

Multivariable-adjusted models were adjusted for age, education, height, total fat mass, lean body mass, parity, smoking status, physical activity, alcohol intake, diabetes, eGFR, tertiles of urinary excretion of calcium (for urinary fluoride) or tertiles of dietary intake of calcium (for dietary fluoride), use of calcium supplements, use of vitamin D supplements, ever use of estrogen and ever use of corticosteroids. Urinary fluoride models were additionally adjusted for serum Beta-CrossLaps (ng/L).

Abbreviations: β : Beta coefficient, BMD: bone mineral density (g/cm²), eGFR: estimated glomerular filtration rate, CI: confidence interval.

Table S7.

Hazard ratios of total, osteoporotic and hip fractures and corresponding 95% confidence intervals by tertiles of urinary fluoride (mg/g creatinine) among women of the Swedish Mammography Cohort – Clinical with complete exposure data.

	Tertiles of urinary fluoride, n = 4,072			p trend
	1	2	3	
All fractures				
Cases	236	251	312	
Person years	11,958	12,773	12,517	
Age-adjusted HR (95 %CI)	Ref.	1.00 (0.83 – 1.19)	1.24 (1.04 – 1.46)	
Multivariable-adjusted HR (95 %CI)	Ref.	0.98 (0.82 – 1.17)	1.17 (0.99 – 1.40)	0.04
Major osteoporotic fractures				
Cases	146	148	204	
Person years	12,543	13,341	13,169	
Age-adjusted HR (95 %CI)	Ref.	0.97 (0.77 – 1.21)	1.30 (1.05 – 1.61)	
Multivariable-adjusted HR (95 %CI)	Ref.	0.94 (0.75 – 1.19)	1.22 (0.98 – 1.52)	0.04
Hip fractures				
Cases	46	49	79	
Person years	13,174	13,964	13,930	
Age-adjusted HR (95 %CI)	Ref.	1.03 (0.69 – 1.55)	1.51 (1.05 – 2.17)	
Multivariable-adjusted HR (95 %CI)	Ref.	1.06 (0.71 – 1.60)	1.51 (1.03 – 2.21)	0.02

Multivariable-adjusted models were adjusted for age, education, height, total fat mass, lean body mass, parity, smoking status, physical activity, alcohol intake, diabetes, eGFR, tertiles of urinary excretion of calcium (for urinary fluoride) or tertiles of dietary intake of calcium (for dietary fluoride), use of calcium supplements, use of vitamin D supplements, ever use of estrogen and ever use of corticosteroids. Urinary fluoride models were additionally adjusted for serum Beta-CrossLaps (ng/L).

Abbreviations: HR: hazard ratio, CI: confidence interval, eGFR: estimated glomerular filtration rate

For each outcome, women contributed with person time from the date of clinical examination until the of date of the specific event studied, death, or end of follow-up at December 31st, 2017.

Table S8.

Cross-sectional mean differences in Bone mineral density (BMD)(β coefficients (95% CI), g/cm^2) across tertiles of urinary fluoride (mg/g creatinine) with BMD at the lumbar spine and femoral neck among women of the Swedish Mammography Cohort – Clinical with urinary creatinine concentrations ranging between 0.3 g/L and 3.0 g/L.

	Tertiles of urinary fluoride, n = 4,164			<i>p</i> trend
	1	2	3	
Lumbar spine				
Age adjusted β (95% CI)	Ref.	-0.014 (-0.028 to 0.000)	-0.021 (-0.036 to -0.007)	
Multivariable adjusted ¹ β (95% CI)	Ref.	0.007 (-0.006 to 0.020)	0.015 (0.001 to 0.028)	0.03
Femoral neck				
Age adjusted β (95% CI)	Ref.	-0.003 (-0.012 to 0.005)	-0.011 (-0.019 to -0.002)	
Multivariable adjusted ¹ β (95% CI)	Ref.	0.007 (-0.001 to 0.015)	0.009 (0.001 to 0.017)	0.03

Multivariable-adjusted models were adjusted for age, education, height, total fat mass, lean body mass, parity, smoking status, physical activity, alcohol intake, diabetes, eGFR, tertiles of urinary excretion of calcium (for urinary fluoride) or tertiles of dietary intake of calcium (for dietary fluoride), use of calcium supplements, use of vitamin D supplements, ever use of estrogen and ever use of corticosteroids. Urinary fluoride models were additionally adjusted for serum Beta-CrossLaps (ng/L)

Abbreviations: β : Beta coefficient, BMD: bone mineral density (g/cm^2), eGFR: estimated glomerular filtration rate, CI: confidence interval.

Table S9.

Hazard ratios of total, osteoporotic and hip fractures and corresponding 95% confidence intervals by tertiles of urinary fluoride (mg/g creatinine) among women of the Swedish Mammography Cohort – Clinical with urinary creatinine concentrations ranging between 0.3 g/L and 3.0 g/L.

	Tertiles of urinary fluoride, n = 4,164			p trend
	1	2	3	
All fractures				
Cases	259	266	296	
Person years	12,745	13,000	12,041	
Age-adjusted HR (95 %CI)	Ref.	1.01 (0.85 – 1.20)	1.19 (1.01 – 1.41)	
Multivariable-adjusted HR ¹ (95 %CI)	Ref.	1.01 (0.84 – 1.19)	1.14 (0.96 – 1.35)	0.11
Major osteoporotic fractures				
Cases	157	161	192	
Person years	13,375	13,580	12,657	
Age-adjusted HR (95 %CI)	Ref.	1.02 (0.82 – 1.28)	1.28 (1.03 – 1.58)	
Multivariable-adjusted HR ¹ (95 %CI)	Ref.	1.01 (0.81 – 1.26)	1.21 (0.97 – 1.50)	0.07
Hip fractures				
Cases	50	54	73	
Person years	14,037	14,240	13,379	
Age-adjusted HR (95 %CI)	Ref.	1.10 (0.75 – 1.62)	1.46 (1.02 – 2.10)	
Multivariable-adjusted HR ¹ (95 %CI)	Ref.	1.15 (0.78 – 1.71)	1.48 (1.02 – 2.16)	0.03

Multivariable-adjusted models were adjusted for age, education, height, total fat mass, lean body mass, parity, smoking status, physical activity, alcohol intake, diabetes, eGFR, tertiles of urinary excretion of calcium (for urinary fluoride) or tertiles of dietary intake of calcium (for dietary fluoride), use of calcium supplements, use of vitamin D supplements, ever use of estrogen and ever use of corticosteroids. Urinary fluoride models were additionally adjusted for serum Beta-CrossLaps (ng/L).

Abbreviations: HR: hazard ratio, CI: confidence interval, eGFR: estimated glomerular filtration rate

For each outcome, women contributed with person time from the date of clinical examination until the of date of the specific event studied, death, or end of follow-up at December 31st, 2017.