SUPPLEMENTAL DATA

Sex-specific association of chronic proton pump inhibitor use with reduced bone density and quality

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Supplementary Table 1. Multivariable linear regression models evaluating the effect of chronic PPI use on TBS and on BMD T-scores at lumbar spine, total hip and femoral neck in men, after the exclusion of patients currently treated with anti-osteoporotic drugs (n=12). Abbreviations: 25OH-VitD, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; CKD G4-G5, chronic kidney disease stage G4-G5; GC, glucocorticoid; N, number; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; TBS, trabecular bone score; β-coeff, β-coefficient.

Model	Lumbar spine TBS (N = 3949)			Lumbar spine T-score (N = 3949)			Total hip T-score (N = 3828)[a]			Femoral neck T-score (N = 3828)[a]		
	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value
Model 1[b]	-0.038	(-0.056, -0.020)	<0.001	-0.24	(-0.46, -0.01)	0.039	-0.20	(-0.38, -0.00)	0.048	-0.21	(-0.42, -0.00)	0.049
Model 2[c]	-0.038	(-0.057, -0.019)	<0.001	-0.26	(-0.50, -0.02)	0.036	-0.20	(-0.41, -0.00)	0.049	-0.22	(-0.43, +0.00)	0.052
Model 3[d]	-0.025	(-0.039, -0.012)	0.001	-	-	-	-	-	-	-	-	-

[a] Missing outcome data in 121 (3.1%) subjects

[b] Adjusted for age, menopausal status, race/ethnicity, income, habitual physical activity, current smoking, BMI, diabetes mellitus, CKD G4-G5, history of liver disease, recent hospitalization (≤ 1 year), dietary calcium intake and 25OH-VitD levels

[c] Adjusted for the same covariates as Model 1, plus current use of hormone-blocking therapy, loop diuretics, thiazide diuretics, NSAIDs, H2-antagonists and history of chronic GC therapy

[d] Adjusted for the same covariates as Model 2, plus lumbar spine T-score and femoral neck T-score

Supplementary Table 2. Multivariable linear regression models evaluating the effect of chronic PPI use on TBS and on BMD T-scores at lumbar spine, total hip and femoral neck in women, after the exclusion of patients currently treated with anti-osteoporotic drugs (n=211). Abbreviations: 25OH-VitD, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; CKD G4-G5, chronic kidney disease stage G4-G5; GC, glucocorticoid; N, number; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; TBS, trabecular bone score; β-coeff, β-coefficient.

Model	Lumbar spine TBS (N = 3306)			Lumbar spine T-score (N = 3306)			Total hip T-score (N = 3150)[a]			Femoral neck T-score (N = 3150)[a]		
	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value
Model 1[a]	-0.005	(-0.018, +0.007)	0.408	-0.02	(-0.25, +0.21)	0.840	+0.06	(-0.09, +0.21)	0.405	+0.03	(-0.12, +0.18)	0.663
Model 2[b]	-0.006	(-0.019, +0.007)	0.326	-0.05	(-0.27, +0.17)	0.653	+0.07	(-0.08, +0.22)	0.349	+0.03	(-0.13, +0.18)	0.733
Model 3[c]	-0.005	(-0.018, +0.009)	0.481	-	-	-	-	-	-	-	-	-

[a] Missing outcome data in 156 (4.7%) subjects

[b] Adjusted for age, menopausal status, race/ethnicity, income, habitual physical activity, current smoking, BMI, diabetes mellitus, CKD G4-G5, history of liver disease, recent hospitalization (≤ 1 year), dietary calcium intake and 25OH-VitD levels

[c] Adjusted for the same covariates as Model 1, plus current use of hormone-blocking therapy, loop diuretics, thiazide diuretics, NSAIDs, H2-antagonists and history of chronic GC therapy

[d] Adjusted for the same covariates as Model 2, plus lumbar spine T-score and femoral neck T-score

Supplementary Table 3. Complete results of the fully adjusted analysis encompassing demographic, clinical, laboratory and medication data as predictors of bone outcomes in men (Table 2, Model 2). Abbreviations: 25OH-VitD, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; CKD G4-G5, chronic kidney disease stage G4-G5; GC, glucocorticoid; N, number; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; ref, reference; TBS, trabecular bone score; β-coeff, β-coefficient.

Parameter	Lumbar spine TBS (N = 3961)			Lumbar spine T-score (N = 3961)			Total hip T-score (N = 3839)			Femoral neck T-score (N = 3839)		
	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value
Chronic PPI use	-0.039	(-0.058, -0.020)	<0.001	-0.27	(-0.51, -0.04)	0.023	-0.21	(-0.41, -0.01)	0.041	-0.22	(-0.44, -0.00)	0.047
Age (per 10 years increase)	-0.027	(-0.029, -0.024)	<0.001	+0.02	(-0.01, +0.05)	0.150	-0.17	(-0.20, -0.15)	<0.001	-0.30	(-0.32, -0.28)	<0.001
Race/ethnicity												
Non-Hispanic White	0 (ref)			0 (ref)			0 (ref)			0 (ref)		
Non-Hispanic Black	+0.020	(+0.008, +0.032)	0.002	+0.72	(+0.61, +0.83)	<0.001	+0.87	(+0.75, +0.99)	<0.001	+0.84	(+0.71, +0.96)	<0.001
Hispanic	+0.008	(-0.002, +0.018)	0.098	-0.26	(-0.37, -0.15)	<0.001	+0.16	(+0.05, +0.28)	0.008	+0.16	(+0.04, +0.28)	0.010
Other	-0.004	(-0.025, +0.017)	0.698	-0.17	(-0.39, +0.05)	0.122	+0.12	(-0.06, +0.30)	0.193	+0.05	(-0.09, +0.20)	0.465
Annual household income												
≥ 75,000 $	0 (ref)			0 (ref)			0 (ref)			0 (ref)		
45,000-74,999 $	-0.011	(-0.022, -0.001)	0.041	+0.05	(-0.06, +0.16)	0.352	-0.05	(-0.14, +0.04)	0.304	-0.02	(-0.12, +0.07)	0.586
20,000-44,999 $	-0.015	(-0.024, -0.006)	0.002	-0.01	(-0.13, +0.11)	0.915	-0.05	(-0.18, +0.07)	0.396	+0.03	(-0.09, +0.16)	0.580
<20,000 $	-0.026	(-0.039, -0.013)	<0.001	-0.03	(-0.21, +0.15)	0.726	-0.05	(-0.19, +0.08)	0.436	+0.04	(-0.10, +0.18)	0.548
Habitual physical activity												
None	0 (ref)			0 (ref)			0 (ref)			0 (ref)		
Moderate	+0.003	(-0.008, +0.014)	0.601	+0.01	(-0.18, +0.19)	0.936	+0.02	(-0.11, +0.15)	0.789	-0.03	(-0.15, +0.09)	0.600
Vigorous	+0.019	(+0.008, +0.031)	0.001	+0.29	(+0.12, +0.46)	0.001	+0.30	(+0.17, +0.43)	<0.001	+0.24	(+0.13, +0.36)	<0.001
Current smoking	-0.019	(-0.027, -0.011)	<0.001	-0.00	(-0.11, +0.11)	0.991	-0.01	(-0.09, +0.06)	0.705	+0.03	(-0.05, +0.11)	0.402
BMI (per 1 kg/m^2 increase)	-0.015	(-0.016, -0.013)	<0.001	+0.07	(+0.06, +0.08)	<0.001	+0.11	(+0.10, +0.12)	<0.001	+0.09	(+0.08, +0.10)	<0.001
Diabetes mellitus	-0.027	(-0.042, -0.011)	0.002	-0.03	(-0.18, +0.12)	0.697	-0.11	(-0.25, +0.03)	0.114	-0.06	(-0.19, +0.08)	0.408
CKD G4-G5	+0.031	(-0.019, +0.081)	0.207	+0.35	(-0.51, +1.20)	0.413	-0.25	(-0.84, +0.35)	0.397	-0.15	(-0.67, +0.37)	0.555
History of liver disease	-0.004	(-0.022, +0.013)	0.603	+0.01	(-0.19, +0.20)	0.946	+0.04	(-0.12, +0.19)	0.634	-0.06	(-0.21, +0.10)	0.459
Recent hospitalization (≤ 1 year)	+0.001	(-0.018, +0.019)	0.951	+0.18	(-0.03, +0.37)	0.084	+0.03	(-0.11, +0.17)	0.686	+0.03	(-0.10, +0.16)	0.595
Dietary calcium intake (per 1 g/day increase)	+0.003	(-0.002, +0.009)	0.181	+0.03	(-0.04, +0.11)	0.353	+0.06	(+0.01, +0.12)	0.017	+0.07	(+0.01, +0.12)	0.023
25OH-VitD (per 10 ng/mL increase)	+0.011	(+0.006, +0.016)	<0.001	+0.08	(+0.02, +0.15)	0.013	+0.14	(+0.08, +0.19)	<0.001	+0.10	(+0.05, +0.15)	0.001
History of chronic GC treatment	-0.013	(-0.045, +0.020)	0.436	-0.02	(-0.40, +0.35)	0.901	-0.28	(-0.58, +0.02)	0.064	-0.13	(-0.43, +0.17)	0.388
Hormone-blocking therapy	-0.043	(-0.097, +0.010)	0.109	-0.67	(-1.00, -0.33)	<0.001	-0.88	(-1.19, -0.58)	<0.001	-0.11	(-0.64, +0.42)	0.678
Loop diuretics	-0.014	(-0.046, +0.017)	0.363	+0.04	(-0.49, +0.58)	0.869	-0.26	(-0.57, +0.05)	0.096	-0.09	(-0.36, +0.19)	0.509
Thiazide diuretics	-0.002	(-0.020, +0.017)	0.868	+0.46	(+0.23, +0.68)	<0.001	+0.14	(-0.07, +0.35)	0.174	+0.15	(-0.03, +0.33)	0.102
NSAIDs	-0.003	(-0.021, +0.016)	0.787	+0.26	(+0.04, +0.47)	0.022	+0.00	(-0.14, +0.14)	0.967	+0.01	(-0.15, +0.16)	0.932
H2-antagonists	-0.003	(-0.035, +0.028)	0.838	-0.10	(-0.68, +0.48)	0.723	-0.15	(-0.44, +0.14)	0.299	-0.14	(-0.47, +0.19)	0.389

Supplementary Table 4. Complete results of the fully adjusted analysis encompassing demographic, clinical, laboratory and medication data as predictors of bone outcomes in women (Table 3, Model 2). Abbreviations: 25OH-VitD, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; CKD G4-G5, chronic kidney disease stage G4-G5; GC, glucocorticoid; N, number; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; ref, reference; TBS, trabecular bone score; β-coeff, β-coefficient.

Parameter	Lumbar spine TBS (N = 3517)			Lumbar spine T-score (N = 3517)			Total hip T-score (N = 3344)			Femoral neck T-score (N = 3344)		
	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value	β-coeff	95%CI	p-value
Chronic PPI use	-0.005	(-0.017, +0.007)	0.427	-0.09	(-0.30, +0.11)	0.345	+0.04	(-0.09, +0.18)	0.511	-0.01	(-0.15, +0.12)	0.845
Age (per 10 years increase)	-0.030	(-0.034, -0.027)	<0.001	-0.14	(-0.20, -0.08)	<0.001	-0.21	(-0.25, -0.17)	<0.001	-0.29	(-0.33, -0.25)	<0.001
Menopausal status												
Pre-menopausal	0 (ref)			0 (ref)			0 (ref)			0 (ref)		
Post-menopausal	-0.056	(-0.068, -0.043)	<0.001	-0.76	(-0.97, -0.56)	<0.001	-0.40	(-0.53, -0.27)	<0.001	-0.36	(-0.50, -0.21)	<0.001
Race/ethnicity												
Non-Hispanic White	0 (ref)			0 (ref)			0 (ref)			0 (ref)		
Non-Hispanic Black	-0.013	(-0.026, -0.001)	0.042	+0.49	(+0.39, +0.60)	<0.001	+0.40	(+0.28, +0.51)	<0.001	+0.54	(+0.45, +0.63)	<0.001
Hispanic	-0.009	(-0.023, +0.005)	0.208	-0.33	(-0.54, -0.12)	0.003	-0.01	(-0.13, +0.12)	0.928	+0.03	(-0.08, +0.13)	0.585
Other	-0.021	(-0.041, -0.001)	0.036	-0.30	(-0.48, -0.12)	0.002	-0.14	(-0.29, +0.02)	0.079	-0.12	(-0.25, +0.02)	0.082
Annual household income												
≥ 75,000 $	0 (ref)			0 (ref)			0 (ref)			0 (ref)		
45,000-74,999 $	+0.003	(-0.007, +0.013)	0.581	+0.04	(-0.08, +0.16)	0.481	-0.07	(-0.16, +0.03)	0.161	-0.08	(-0.17, +0.01)	0.094
20,000-44,999 $	-0.014	(-0.024, -0.003)	0.012	-0.15	(-0.28, -0.02)	0.030	-0.13	(-0.24, -0.03)	0.015	-0.09	(-0.18, +0.00)	0.059
<20,000 $	-0.028	(-0.038, -0.017)	<0.001	-0.30	(-0.45, -0.15)	<0.001	-0.25	(-0.35, -0.15)	<0.001	-0.21	(-0.30, -0.11)	<0.001
Habitual physical activity												
None	0 (ref)			0 (ref)			0 (ref)			0 (ref)		
Moderate	+0.005	(-0.003, +0.014)	0.208	-0.01	(-0.14, +0.11)	0.810	+0.03	(-0.06, +0.12)	0.536	+0.00	(-0.08, +0.08)	0.973
Vigorous	+0.004	(-0.005, +0.012)	0.424	-0.03	(-0.19, +0.14)	0.726	+0.03	(-0.08, +0.15)	0.543	+0.00	(-0.12, +0.12)	0.969
Current smoking	-0.017	(-0.025, -0.009)	<0.001	-0.01	(-0.11, +0.08)	0.762	-0.14	(-0.22, -0.06)	0.002	-0.07	(-0.17, +0.03)	0.151
BMI (per 1 kg/m² increase)	-0.006	(-0.007, -0.006)	<0.001	+0.07	(+0.06, +0.08)	<0.001	+0.10	(+0.09, +0.10)	<0.001	+0.08	(+0.08, +0.09)	<0.001
Diabetes mellitus	-0.013	(-0.025, -0.001)	0.040	+0.29	(+0.11, +0.47)	0.002	+0.20	(+0.05, +0.34)	0.009	+0.23	(+0.10, +0.36)	0.001
CKD G4-G5	-0.002	(-0.041, +0.037)	0.929	-0.25	(-0.67, +0.18)	0.245	-0.53	(-0.89, -0.17)	0.005	-0.32	(-0.69, +0.05)	0.088
History of liver disease	-0.013	(-0.034, +0.008)	0.213	-0.20	(-0.49, +0.08)	0.148	-0.13	(-0.30, +0.03)	0.111	-0.16	(-0.32, -0.00)	0.045
Recent hospitalization (≤ 1 year)	+0.000	(-0.012, +0.013)	0.981	-0.08	(-0.23, +0.08)	0.313	-0.11	(-0.24, +0.01)	0.069	-0.07	(-0.19, +0.04)	0.213
Dietary calcium intake (per 1 g/day increase)	+0.007	(+0.001, +0.012)	0.021	+0.09	(+0.03, +0.15)	0.003	+0.11	(+0.04, +0.18)	0.003	+0.09	(+0.02, +0.16)	0.016
25OH-VitD (per 10 ng/mL increase)	+0.006	(+0.001, +0.011)	0.014	+0.03	(-0.01, +0.08)	0.153	+0.04	(+0.00, +0.08)	0.033	+0.06	(+0.02, +0.10)	0.008
History of chronic GC treatment	+0.006	(-0.012, +0.023)	0.495	+0.12	(-0.16, +0.41)	0.384	-0.05	(-0.27, +0.17)	0.638	-0.08	(-0.29, +0.13)	0.452
Hormone-blocking therapy	-0.012	(-0.053, +0.030)	0.573	+0.38	(-0.11, +0.87)	0.127	+0.19	(-0.19, +0.58)	0.317	+0.09	(-0.37, +0.55)	0.687
Loop diuretics	-0.024	(-0.069, +0.021)	0.285	+0.02	(-0.47, +0.51)	0.931	-0.45	(-0.77, -0.13)	0.007	-0.19	(-0.50, +0.12)	0.215
Thiazide diuretics	+0.011	(-0.004, +0.027)	0.147	+0.28	(+0.10, +0.47)	0.003	+0.05	(-0.07, +0.17)	0.389	+0.08	(-0.02, +0.19)	0.128
NSAIDs	+0.005	(-0.010, +0.020)	0.520	+0.02	(-0.18, +0.22)	0.845	+0.01	(-0.23, +0.24)	0.947	+0.02	(-0.17, +0.21)	0.838
H2-antagonists	+0.012	(-0.011, +0.036)	0.298	+0.09	(-0.21, +0.39)	0.544	+0.06	(-0.24, +0.36)	0.697	+0.12	(-0.15, +0.38)	0.370