SUPPLEMENTAL TABLES FOR

Effect of vitamin D supplementation or fortification on bone turnover markers in women: A systematic review and meta-analysis

Nasrin Nasimi[1,2], Sanaz Jamshidi[3], Aida Askari[1], Nazanin Zolfaghari[1], Erfan Sadeghi[4], Mehran Nouri[1], Nick Bellissimo[5], Shiva Faghih[2*]

[1] Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

[2] Department of Community Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

[3] Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran.

[4] Research Consultation Center (RCC), Shiraz University of Medical Sciences, Shiraz, Iran.

[5] Toronto Metropolitan University, School of Nutrition, Toronto, ON M5B-2K3

Table S1. Summary findings of comparison of uNTX between the study treatments.

Outcomes	N	Subgroup Analysis		Meta-Regression 1	Meta-Regression 2	Non-linear Meta Regression
		MD (95%CI), *P-value*	**I^2, *P-value***	**B (95% CI), *P-value*, Res I^2**	**B (95% CI), *P-value*, Res I^2**	**S or NS**
Total	6	- 8.138 (- 12.864, -3.413), ***0.001***	**0.0%**, *0.627*			
Dose ≤ 600 IU/day		NA		Ref	0.0091 (-0.0050, 0.0232), *0.206*, 0.00%	NS
Dose > 600 IU/day				6.9042 (-3.736, 17.544), *0.203*, 0.00%		
Duration ≤ 12weeks	3	- 7.195 (- 13.050, -1.341), ***0.016***	**12.2%**, *0.345*	Ref	-0.0044 (-0.1653, 0.1565), *0.957*, 1.88%	NS
Duration > 12weeks	3	- 10.84 (- 20.193, - 1.488), ***0.023***	**0.0%**, *0.634*	-3.6285 (-14.466, 7.209), *0.512*, 0.00%		
Baseline vitD ≤ 20ng/ml		NA		NA	0.5277 (-2.3559, 3.4114), *0.720*, 2.18%	NS
Baseline vitD > 20ng/ml						
Age ≤ 60 years		NA		NA	0.0236 (-0.4875, 0.5348), *0.904*, 0.00%	NS
Age > 60 years						
Publication year < 2010		NA		NA	0.6358 (-0.6248, 1.8964), *0.323*, 0.00%	NS
Publication year ≥ 2010						
Sample Size ≤ 100		NA		NA	-0.0435 (-0.1909, 0.1038), *0.563*, 0.00%	NS
Sample Size > 100						
Healthy postmeno		NA		NA	NA	NA
Postmeno osteoporosis						
Region		NA		NA	NA	NA
Asia						
Europe						
America						
South America, Australia						
Risk of bias		NA		NA	NA	NA
High						
Some Concerns						
Low						

Meta-Regression 1: the subgrouping variable was included into the model as a categorized variable. **Meta-Regression 2**: the subgrouping variable was included into the model as a continuous variable. **Abbreviations**: N; Number of included interventions, B; Beta coefficient reflecting the effect of the subgrouping variable on the pooled effect size. vit; vitamin, postmeno; post-menopausal, CI; confidence interval, Res $I^{2;}$ Residual I^2, NA; Not Applicable, S; Singnificant, NS; Non-significant. *Italic*; P-values; **Bold**; significant P-value.

Table S2. Summary findings of comparison of BALP between the study treatments.

Outcomes	N	Subgroup Analysis		Meta-Regression 1	Meta-Regression 2	Non-linear Meta Regression
		MD (95%CI), *P-value*	**I^2, *P-value***	**B (95% CI), *P-value*, Res I^2**	**B (95% CI), *P-value*, Res I^2**	**S or NS**
Total	6	- 1.487 (- 9.772, 6.797), *0.725*	95.3%, *<0.001*			
Dose ≤ 600 IU/day	4	-5.425 (-14.417. 3.568), *0.237*	71.1%, *0.058*	Ref	0.0121 (-0.0097, 0.0340), 0.276, 94.04%	NS
Dose > 600 IU/day	2	5.058 (-8.760, 18.876), *0.473*	97.6%, *<0.001*	10.941 (-5.068, 26.950), *0.180*, 91.42%		
Duration ≤ 12weeks		NA		NA	-0.0806 (-0.4326, 0.2712), *0.653*, 93.98%	NS
Duration > 12weeks						
Baseline vitD ≤ 20ng/ml	2	-11.496 (-33.484, 10.492), *0.305*	82.5%, *0.017*	Ref	0.6681 (-3.1657, 4.5021), *0.733*, 96.61%	NS
Baseline vitD > 20ng/ml	3	1.761 (-10.280, 13.801), *0.774*	96.7%, *<0.001*	12.071 (-10.016, 34.160), *0.284*, 96.43%)		
Age ≤ 60 years		NA		NA	-0.8261 (-2.0006, 0.3482), *0.168*, 90.51%	NS
Age > 60 years						
Publication year < 2010	3	-6.354 (-19.767, 7.058), *0.353*	86.9%, *0.025*	Ref	0.6212 (-0.5198, 1.7622), *0.286*, 91.82%	NS
Publication year ≥2010	3	2.729 (-8.447, 13.904), *0.632*	94.5%, *<0.001*	8.6549 (-8.294, 25.604), *0.317*, 92.59%		
Sample Size ≤ 100	3	-7.807 (-23.833, 8.219), 0.340	72.3%, *0.025*	Ref	0.0288 (-0.0841, 0.1417), *0.617*, 95.10%	NS
Sample Size > 100	3	2.004 (-7.917, 11.924), 0.692	97.6%, *<0.001*	9.2874 (-8.516, 27.090), *0.307*, 96.46%		
Healthy postmeno		NA		NA	NA	NA
Postmeno osteoporosis						
Region		NA		NA	NA	NA
Asia						
Europe						
America						
South America, Australia						
Risk of bias		NA		NA	NA	NA
High						
Some Concerns						
Low						

Meta-Regression 1: the subgrouping variable was included into the model as a categorized variable. **Meta-Regression 2**: the subgrouping variable was included into the model as a continuous variable. **Abbreviations**: N; Number of included interventions, B; Beta coefficient reflecting the effect of the subgrouping variable on the pooled effect size. vit; vitamin, postmeno; post-menopausal, CI; confidence interval, Res $I^{2;}$ Residual I^2, NA; Not Applicable, S; Singnificant, NS; Non-significant. *Italic*; P-values; **Bold**; significant P-value.

Table S3 GRADE evidence profile rating for the change in bone turnover markers in studies testing vitamin D supplementation in women.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	vitamin D supplementation	control	Relative (95% CI)	Absolute (95% CI)		
Overall effects of vitamin D supplementation on changes in sCTX level (All RCTs) (assessed with: MD)												
15	randomized trials	not serious	serious[a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect dose response gradient	1196	1453	-	MD **0.038 lower** (0.058 lower to 0.018 lower)	⊕⊕⊕⊕ High	IMPORTANT
Overall effects of vitamin D supplementation on changes in uNTX level (All RCTs) (assessed with: MD)												
4	randomized trials	very serious[e]	not serious	not serious	not serious	very strong association	167	167	-	MD **8.188 lower** (12.898 lower to 3.479 lower)	⊕⊕⊕⊕ High	IMPORTANT
Overall effects of vitamin D supplementation on changes in OC level (All RCTs) (assessed with: MD)												
18	randomized trials	very serious[b]	very serious[c]	not serious	not serious	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient	983	1140	-	MD **0.61 lower** (1.151 lower to 0.07 lower)	⊕⊕⊕◯ Moderate	IMPORTANT
Overall effects of vitamin D supplementation on changes in P1NP level (All RCTs) (assessed with: MD)												
11	randomized trials	not serious	serious[d]	not serious	not serious	dose response gradient	1007	1292	-	MD **0.191 lower** (2.186 lower to 1.803 higher)	⊕⊕⊕⊕ High	IMPORTANT
Overall effects of vitamin D supplementation on changes in BALP level (All RCTs) (assessed with: MD)												
6	randomized trials	very serious[f]	very serious[g]	not serious	not serious	very strong association	416	403	-	MD **1.253 lower** (8.888 lower to 6.381 higher)	⊕⊕◯◯ Low	IMPORTANT

CI: confidence interval; MD: mean difference. Explanations: a. I2= 67.3 %, b. 27.7% of included studies had high risk of bias., c. I2= 80.3%, d. I2= 58.5%, e. 25% of included studies had high risk of bias., f. 33.3% of included studies had high risk of bias., g. I2= 94.5%.

SUPPLEMENTAL FIGURES FOR

Effect of vitamin D supplementation or fortification on bone turnover markers in women: A systematic review and meta-analysis

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[1] Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

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[4] Research Consultation Center (RCC), Shiraz University of Medical Sciences, Shiraz, Iran.

[5] Toronto Metropolitan University

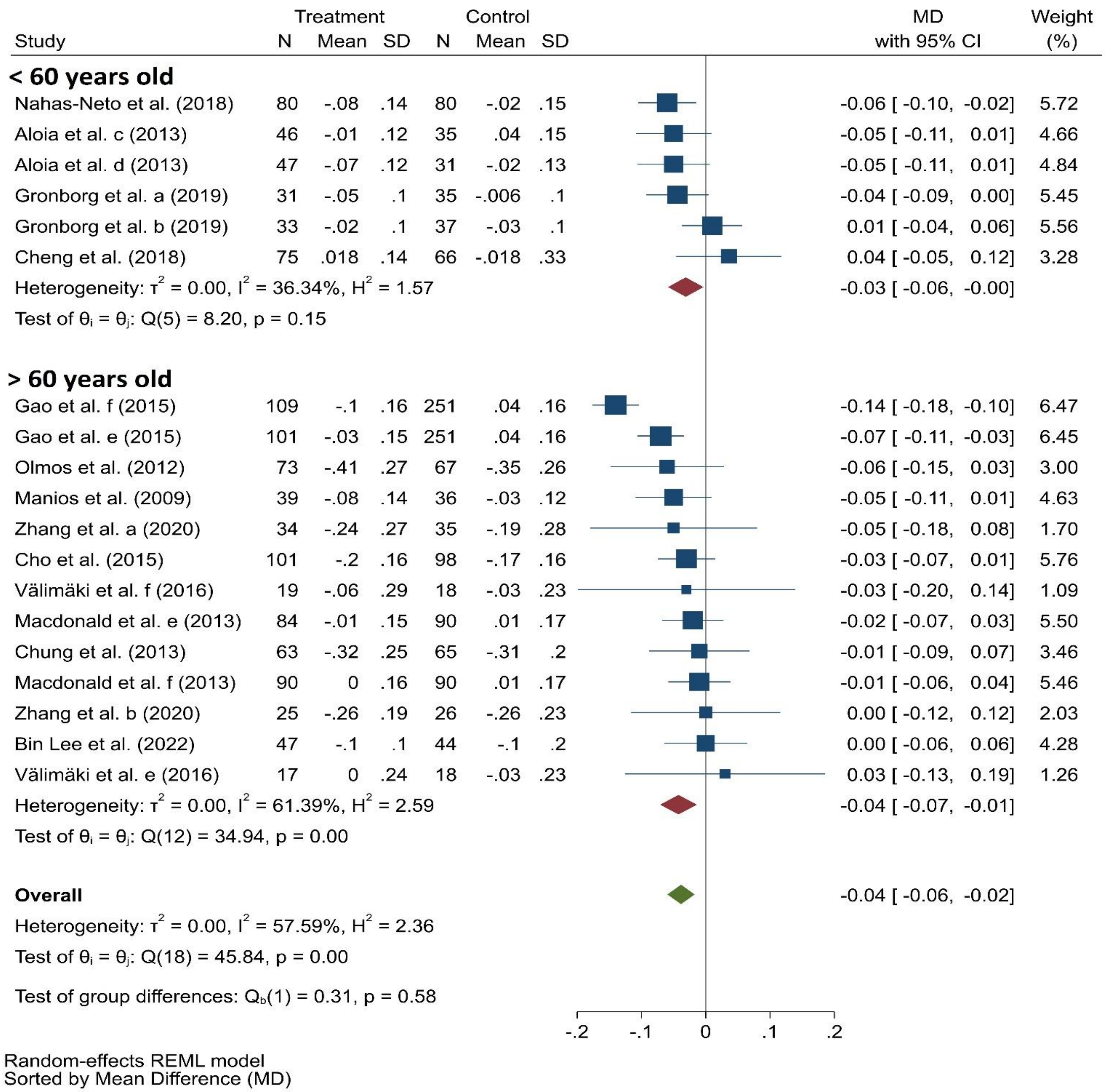
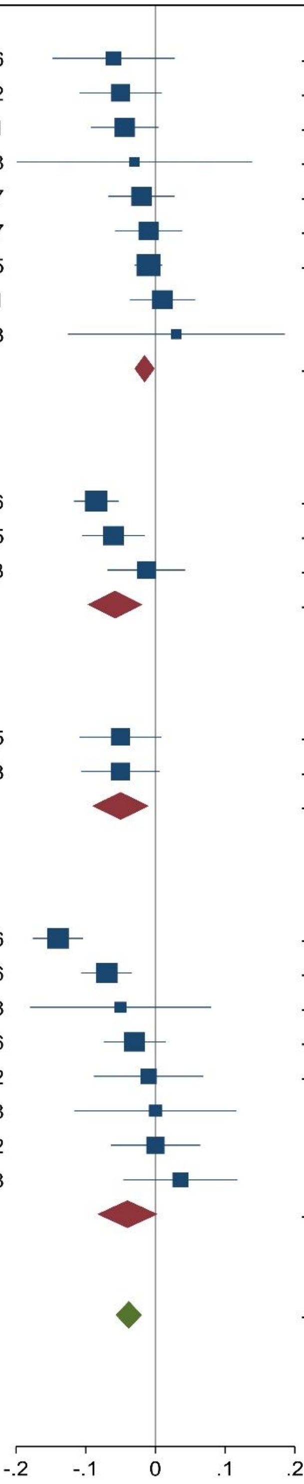


Figure S1. Forest plot of the Randomized Clinical Trials (RCTs) examining the effect of vitamin D supplementation on sCTX (subgrouping participants' age). Data have been expressed as mean differences (MDs) between intervention and control groups with 95% confidence intervals (CIs). Estimates were pooled using the random effects model. Letters between parentheses represent: a, b: different participant groups; c, d: different intervention/ control groups; e, f: different dose of vitamin D.

Study	Treatment N	Treatment Mean	Treatment SD	Control N	Control Mean	Control SD	MD with 95% CI	Weight (%)
Europe								
Olmos et al. (2012)	73	-.41	.27	67	-.35	.26	-0.06 [-0.15, 0.03]	3.00
Manios et al. (2009)	39	-.08	.14	36	-.03	.12	-0.05 [-0.11, 0.01]	4.63
Gronborg et al. a (2019)	31	-.05	.1	35	-.006	.1	-0.04 [-0.09, 0.00]	5.45
Välimäki et al. f (2016)	19	-.06	.29	18	-.03	.23	-0.03 [-0.20, 0.14]	1.09
Macdonald et al. e (2013)	84	-.01	.15	90	.01	.17	-0.02 [-0.07, 0.03]	5.50
Macdonald et al. f (2013)	90	0	.16	90	.01	.17	-0.01 [-0.06, 0.04]	5.46
Bislev et al. (2019)	40	.01	.04	41	.02	.05	-0.01 [-0.03, 0.01]	7.73
Gronborg et al. b (2019)	33	-.02	.1	37	-.03	.1	0.01 [-0.04, 0.06]	5.56
Välimäki et al. e (2016)	17	0	.24	18	-.03	.23	0.03 [-0.13, 0.19]	1.26
Heterogeneity: τ^2 = 0.00, I^2 = 0.01%, H^2 = 1.00							-0.02 [-0.03, -0.00]	
Test of $\theta_i = \theta_j$: Q(8) = 5.49, p = 0.70								
South America & Australia								
von Hurst et al. b (2010)	13	-.03	.037	13	.055	.046	-0.09 [-0.12, -0.05]	6.80
Nahas-Neto et al. (2018)	80	-.08	.14	80	-.02	.15	-0.06 [-0.10, -0.02]	5.72
von Hurst et al. a (2010)	29	-.011	.108	26	.002	.103	-0.01 [-0.07, 0.04]	4.87
Heterogeneity: τ^2 = 0.00, I^2 = 59.38%, H^2 = 2.46							-0.06 [-0.10, -0.02]	
Test of $\theta_i = \theta_j$: Q(2) = 4.86, p = 0.09								
America								
Aloia et al. c (2013)	46	-.01	.12	35	.04	.15	-0.05 [-0.11, 0.01]	4.66
Aloia et al. d (2013)	47	-.07	.12	31	-.02	.13	-0.05 [-0.11, 0.01]	4.84
Heterogeneity: τ^2 = 0.00, I^2 = 0.02%, H^2 = 1.00							-0.05 [-0.09, -0.01]	
Test of $\theta_i = \theta_j$: Q(1) = 0.00, p = 1.00								
Asia								
Gao et al. f (2015)	109	-.1	.16	251	.04	.16	-0.14 [-0.18, -0.10]	6.47
Gao et al. e (2015)	101	-.03	.15	251	.04	.16	-0.07 [-0.11, -0.03]	6.45
Zhang et al. a (2020)	34	-.24	.27	35	-.19	.28	-0.05 [-0.18, 0.08]	1.70
Cho et al. (2015)	101	-.2	.16	98	-.17	.16	-0.03 [-0.07, 0.01]	5.76
Chung et al. (2013)	63	-.32	.25	65	-.31	.2	-0.01 [-0.09, 0.07]	3.46
Zhang et al. b (2020)	25	-.26	.19	26	-.26	.23	0.00 [-0.12, 0.12]	2.03
Bin Lee et al. (2022)	47	-.1	.1	44	-.1	.2	0.00 [-0.06, 0.06]	4.28
Cheng et al. (2018)	75	.018	.14	66	-.018	.33	0.04 [-0.05, 0.12]	3.28
Heterogeneity: τ^2 = 0.00, I^2 = 75.71%, H^2 = 4.12							-0.04 [-0.08, 0.00]	
Test of $\theta_i = \theta_j$: Q(7) = 32.06, p = 0.00								
Overall							-0.04 [-0.06, -0.02]	
Heterogeneity: τ^2 = 0.00, I^2 = 64.28%, H^2 = 2.80								
Test of $\theta_i = \theta_j$: Q(21) = 64.29, p = 0.00								
Test of group differences: $Q_b(3)$ = 6.23, p = 0.10								



Random-effects REML model
Sorted by Mean Difference (MD)

Figure S2. Forest plot of the Randomized Clinical Trials (RCTs) examining the effect of vitamin D supplementation on sCTX (subgrouping region). Data have been expressed as mean differences (MDs) between intervention and control groups with 95% confidence intervals (CIs). Estimates were pooled using the random effects model. Letters between parentheses represent: a, b: different participant groups; c, d: different intervention/ control groups; e, f: different dose of vitamin D.

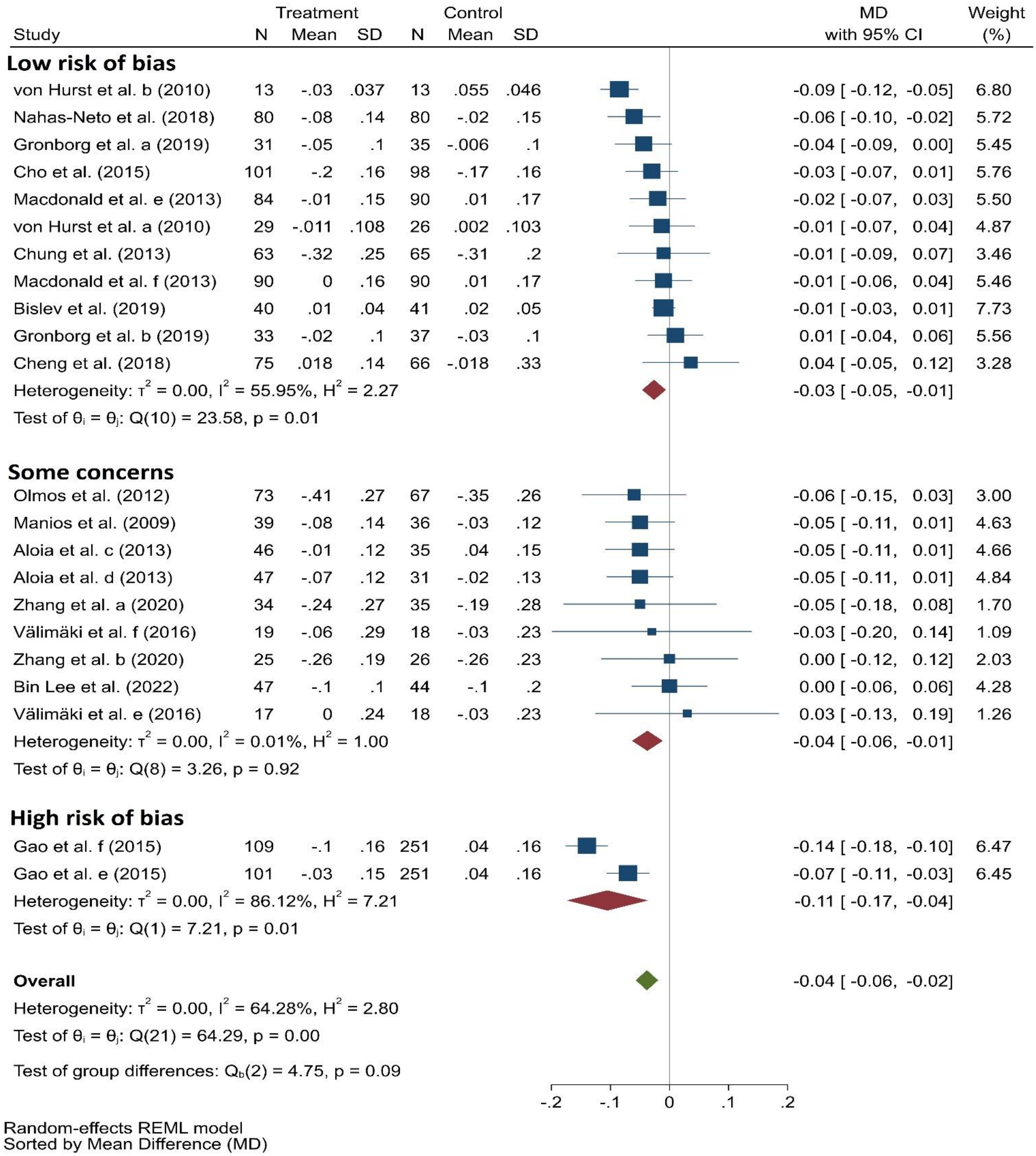


Figure S3. Forest plot of the Randomized Clinical Trials (RCTs) examining the effect of vitamin D supplementation on sCTX (subgrouping quality of studies). Data have been expressed as mean differences (MDs) between intervention and control groups with 95% confidence intervals (CIs). Estimates were pooled using the random effects model. Letters between parentheses represent: a, b: different participant groups; c, d: different intervention/ control groups; e, f: different dose of vitamin D.

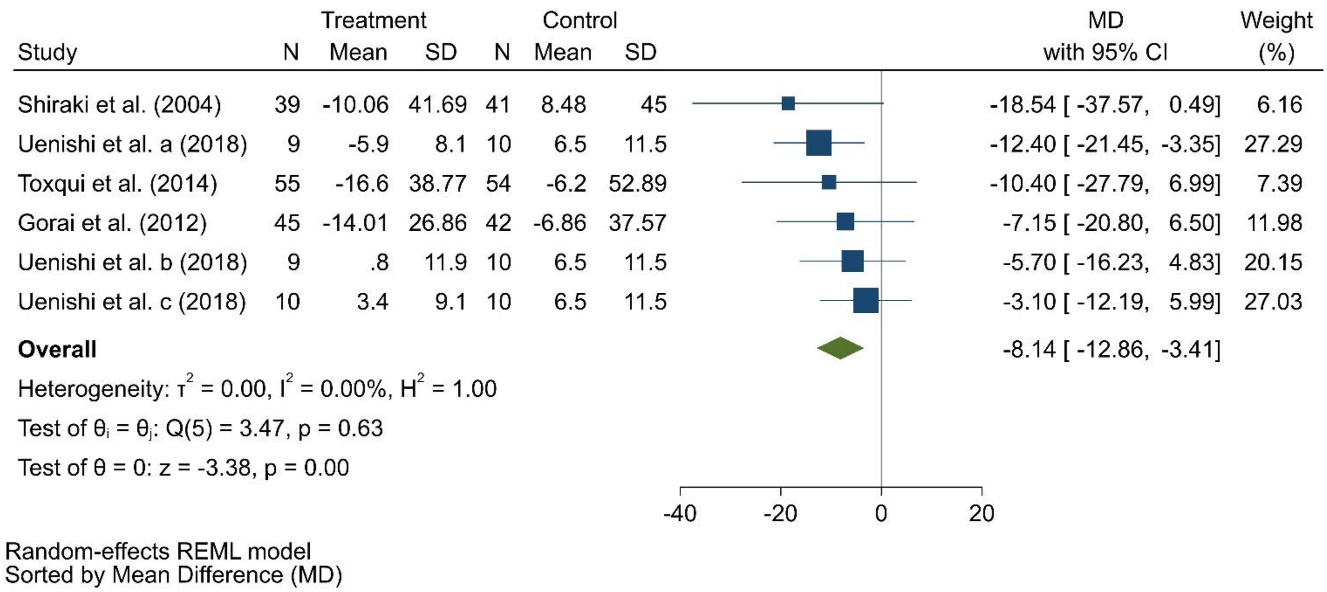


Figure S4. Forest plot of the Randomized Clinical Trials (RCTs) examining the effect of vitamin D supplementation on uNTX. Data have been expressed as mean differences (MDs) between intervention and control groups with 95% confidence intervals (CI). Estimates were pooled using the fixed effects model. Letters between parentheses represent: a, b, d: different dose of vitamin D.

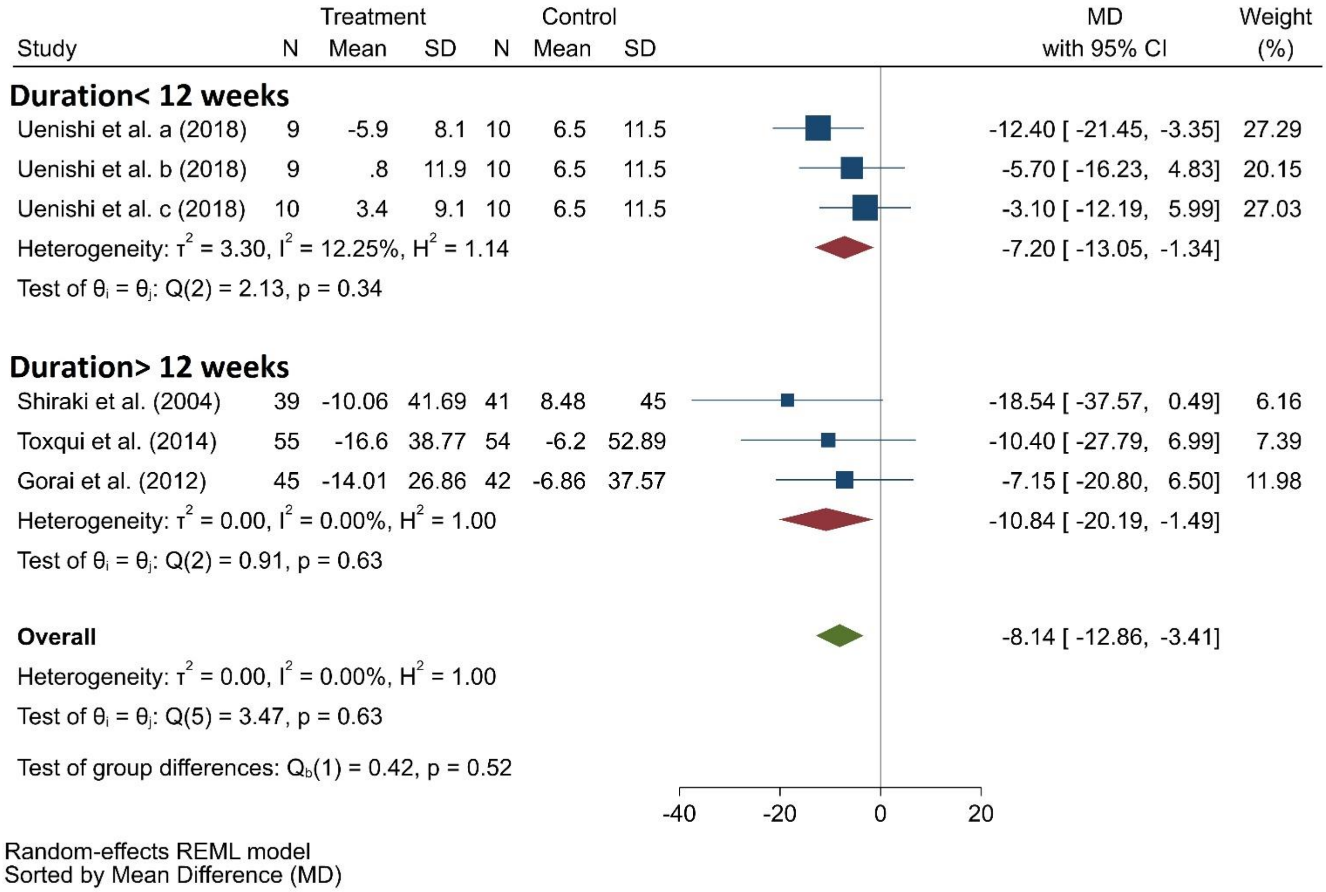


Figure S5. Forest plot of the Randomized Clinical Trials (RCTs) examining the effect of vitamin D supplementation on uNTX (subgrouping study duration). Data have been expressed as mean differences (MDs) between intervention and control groups with 95% confidence intervals (CI). Estimates were pooled using the fixed effects model. Letters between parentheses represent: a, b, d: different dose of vitamin D.

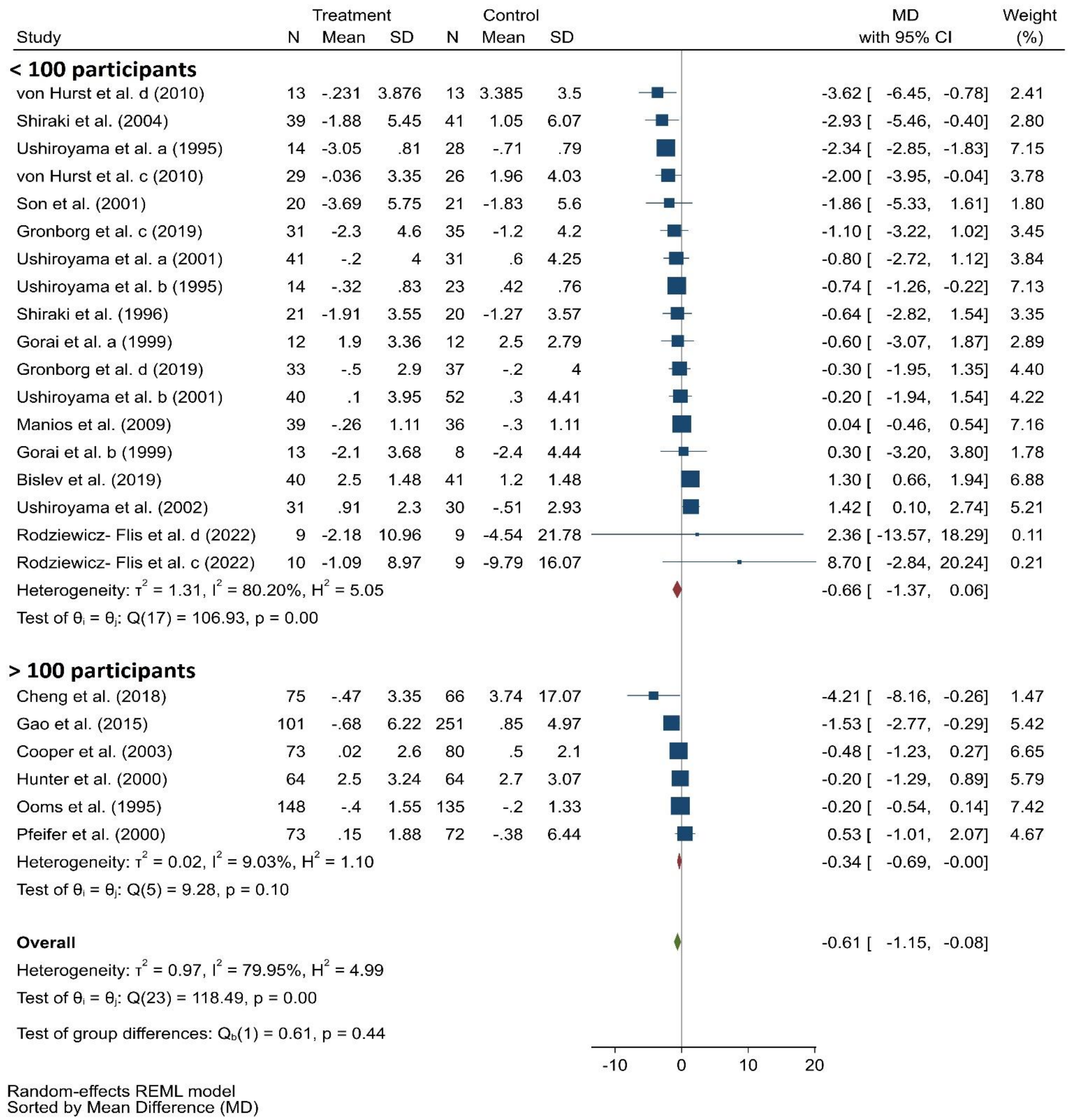


Figure S6. Forest plot of the Randomized Clinical Trials (RCTs) examining the effect of vitamin D supplementation on OC (subgrouping study sample size). Data have been expressed as mean differences (MDs) between intervention and control groups with 95% confidence intervals (CI). Estimates were pooled using the random effects model. Letters between parentheses represent: a, b: different intervention/ control groups; c, d: different participant groups.

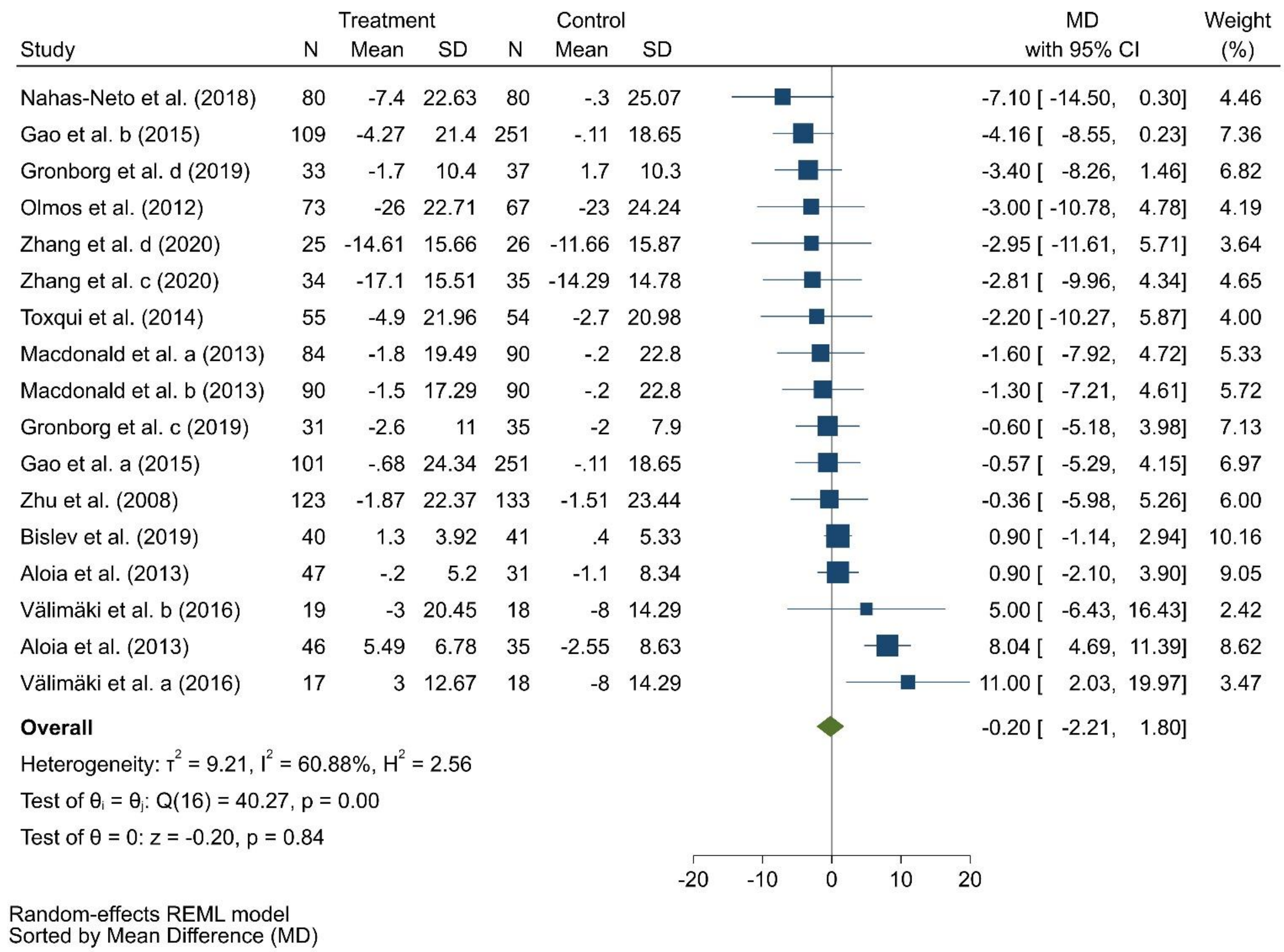


Figure S7. Forest plot of the Randomized Clinical Trials (RCTs) examining the effect of vitamin D supplementation on P1NP. Data have been expressed as mean differences (MDs) between intervention and control groups with 95% confidence intervals (CI). Estimates were pooled using the random effects model. Letters between parentheses represent: a, b: different dose of vitamin D; c, d: different participant groups.

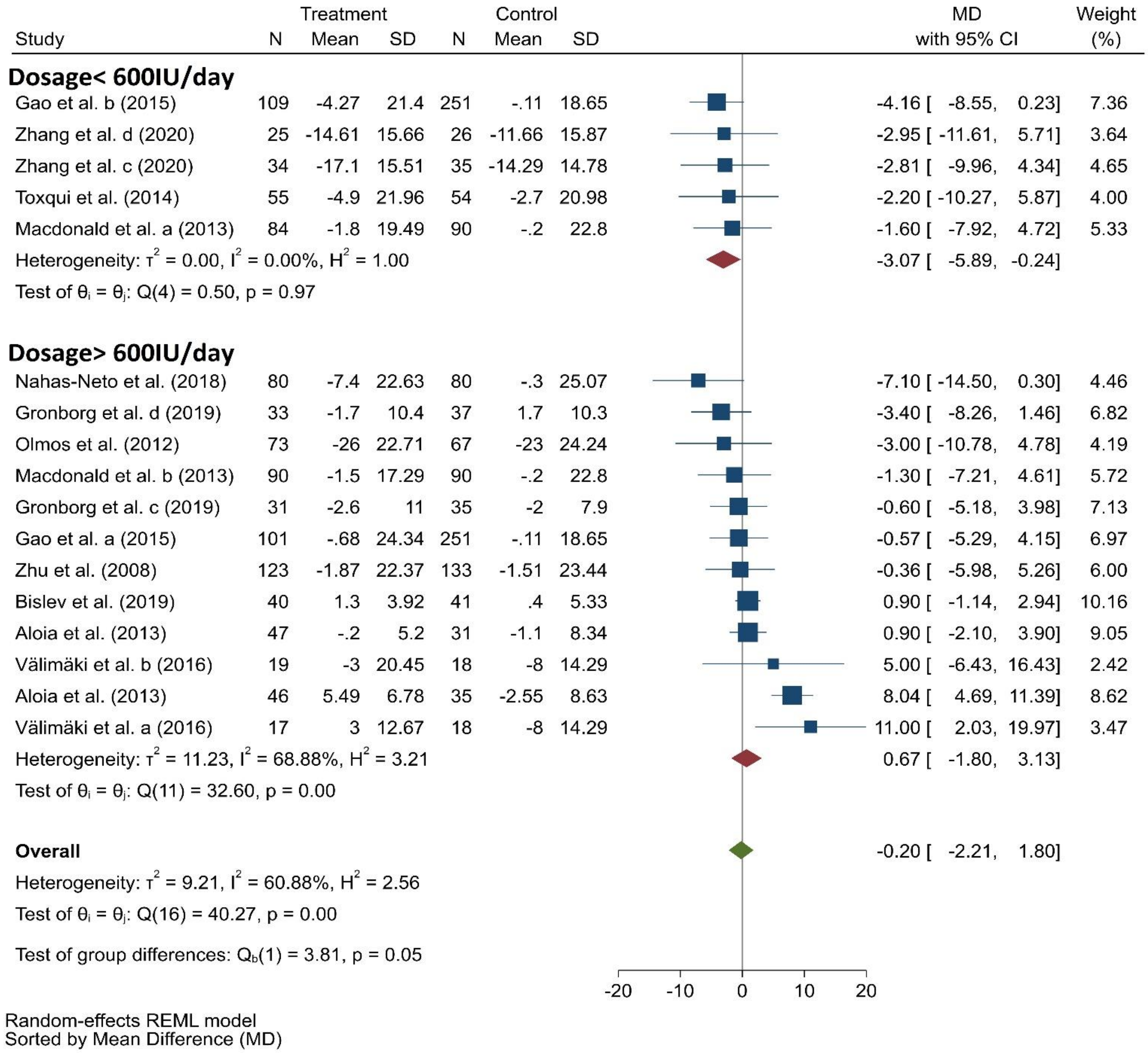


Figure S8. Forest plot of the Randomized Clinical Trials (RCTs) examining the effect of vitamin D supplementation on P1NP (subgrouping dosage of supplementation). Data have been expressed as mean differences (MDs) between intervention and control groups with 95% confidence intervals (CI). Estimates were pooled using the random effects model. Letters between parentheses represent: a, b: different dose of vitamin D; c, d: different participant groups.

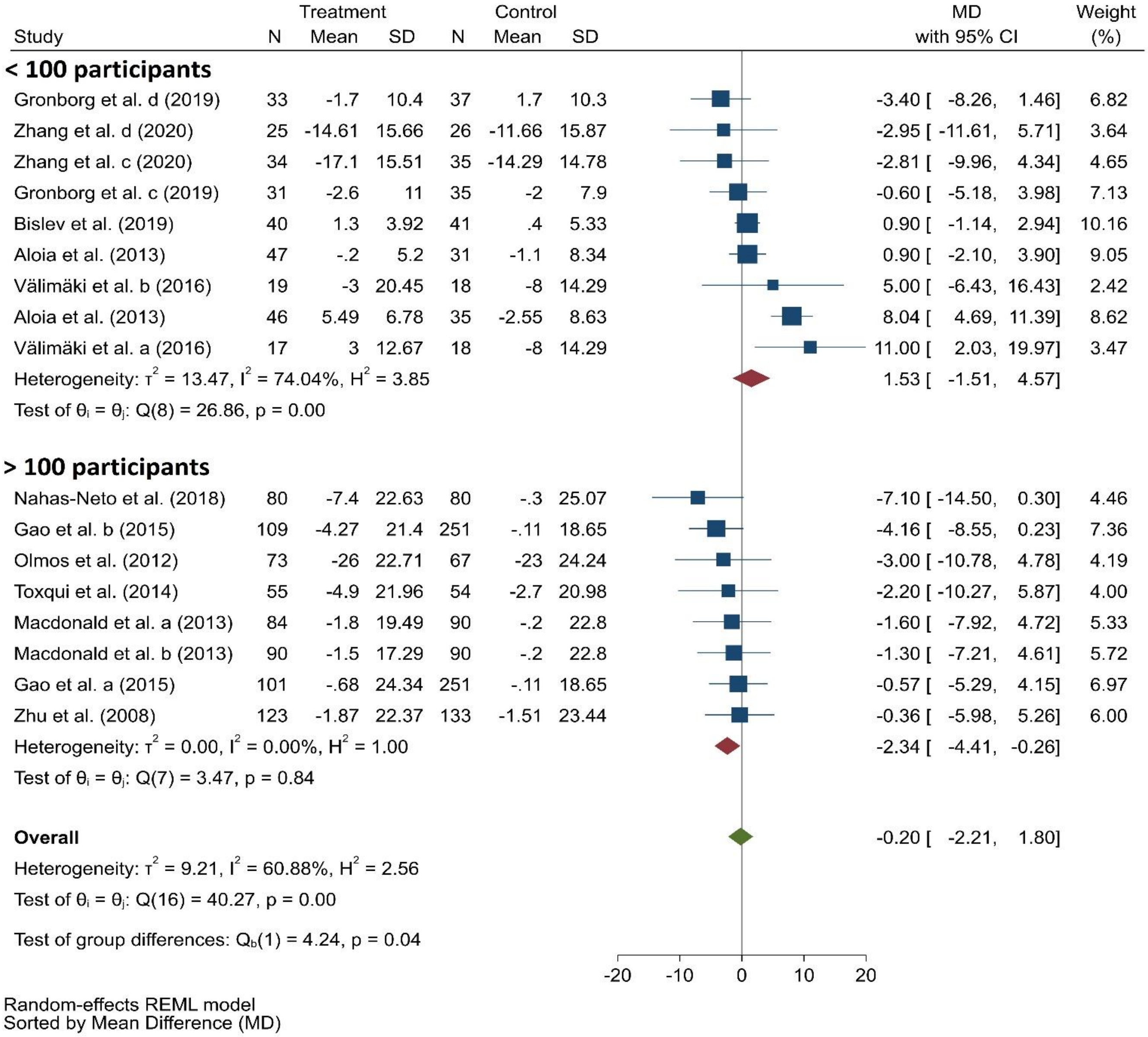


Figure S9. Forest plot of the Randomized Clinical Trials (RCTs) examining the effect of vitamin D supplementation on P1NP (subgrouping study sample size). Data have been expressed as mean differences (MDs) between intervention and control groups with 95% confidence intervals (CI). Estimates were pooled using the random effects model. Letters between parentheses represent: a, b: different dose of vitamin D; c, d: different participant groups.

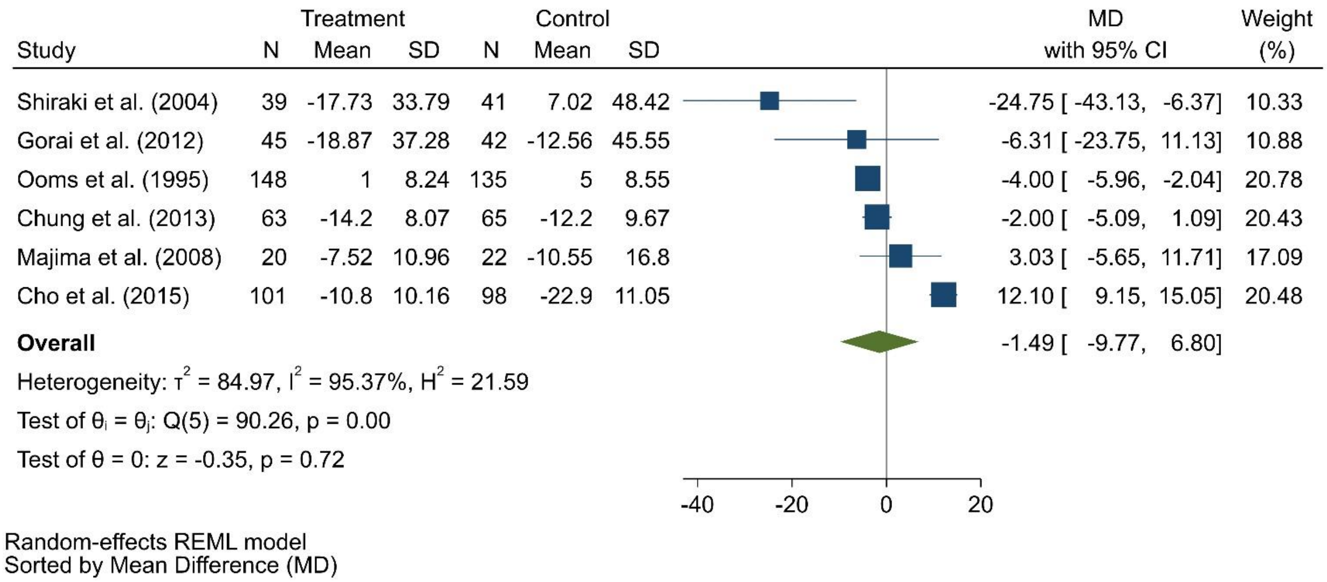


Figure S10. Forest plot of the Randomized Clinical Trials (RCTs) examining the effect of vitamin D supplementation on BALP. Data have been expressed as mean differences (MDs) between intervention and control groups with 95% confidence intervals (CI). Estimates were pooled using the random effects model.

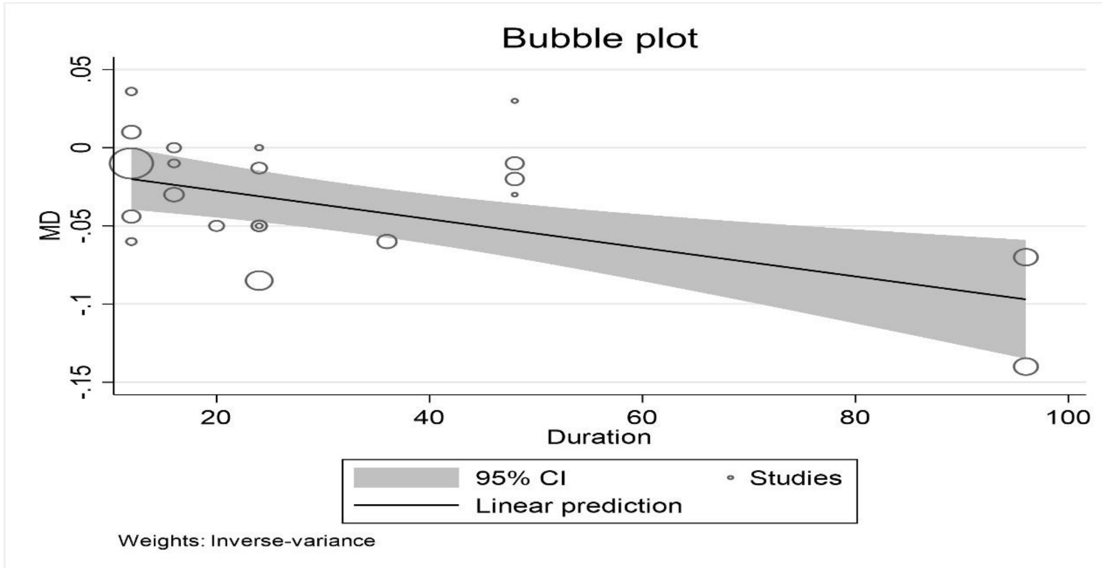


Figure S11. Meta-regression analysis revealed a significant association between sCTX level and study duration.

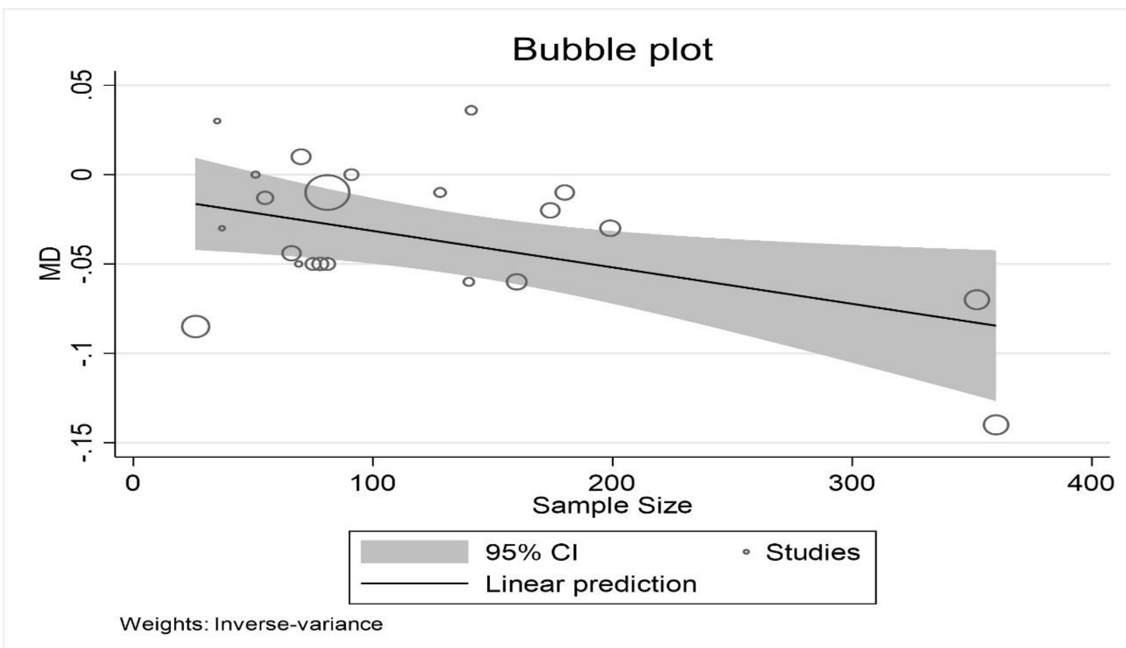


Figure S12. Meta-regression analysis revealed a significant association between sCTX level and study sample size.

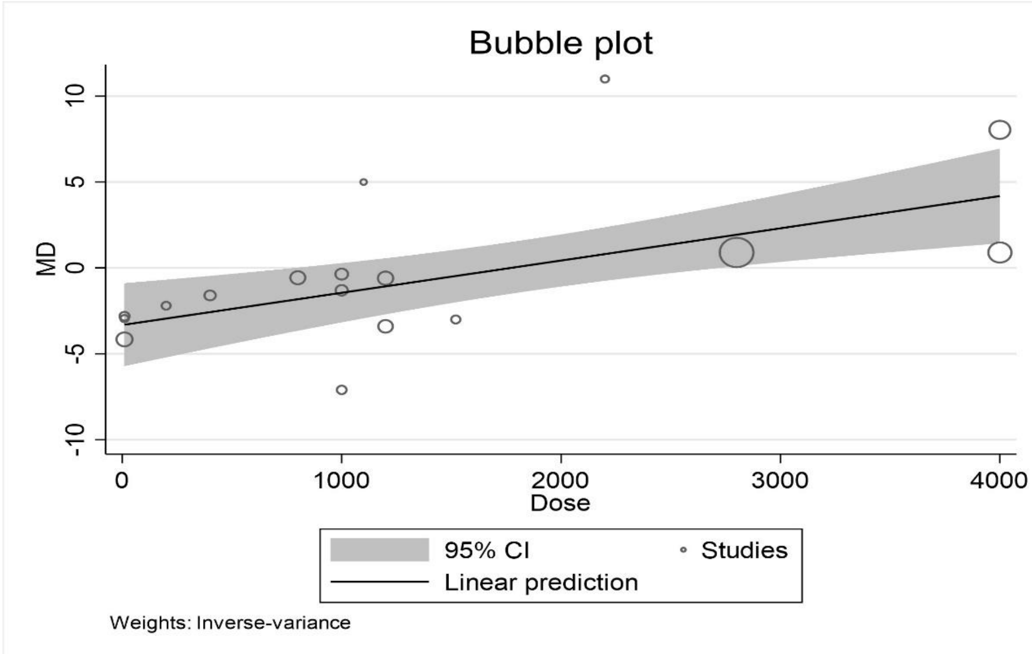


Figure S13. Meta-regression analysis revealed a significant association between P1NP level and dosage of vitamin D supplementation.

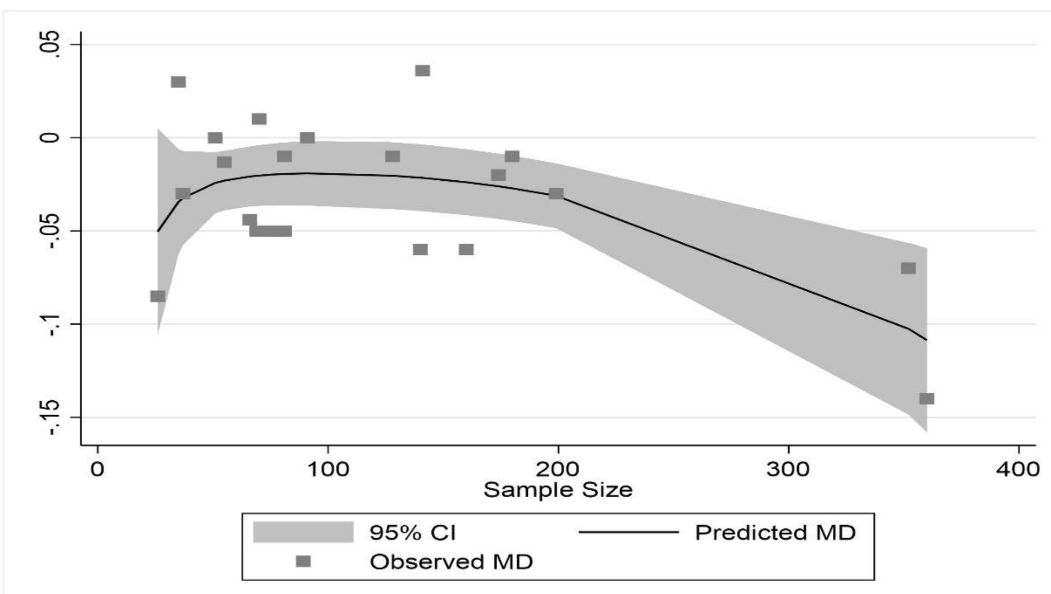


Figure S14. Non-linear meta-regression analysis revealed a significant association between sCTX level and study sample size.

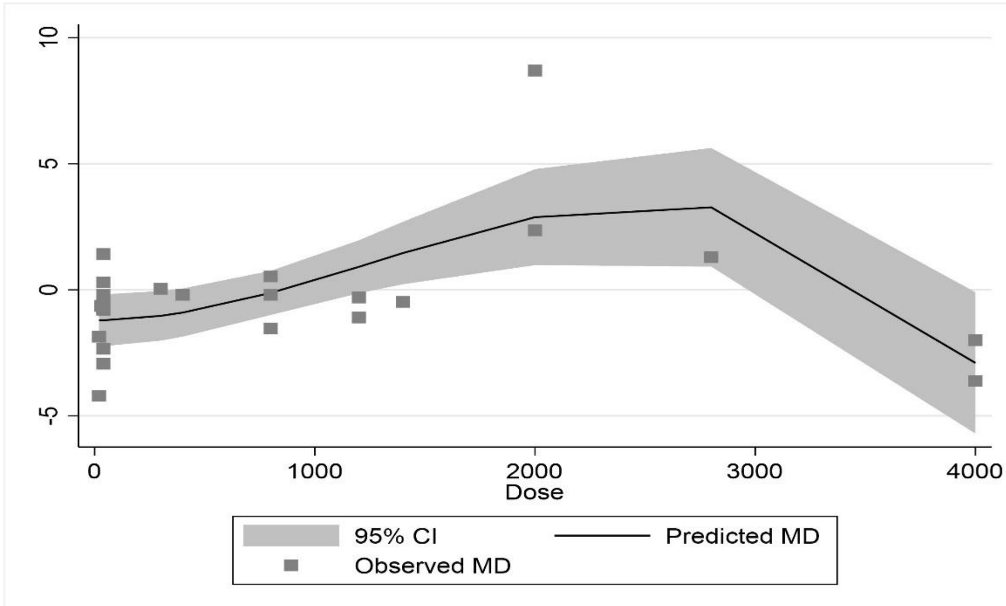


Figure S15. Non-linear meta-regression analysis revealed a significant association between OC level and dosage of vitamin D supplementation.

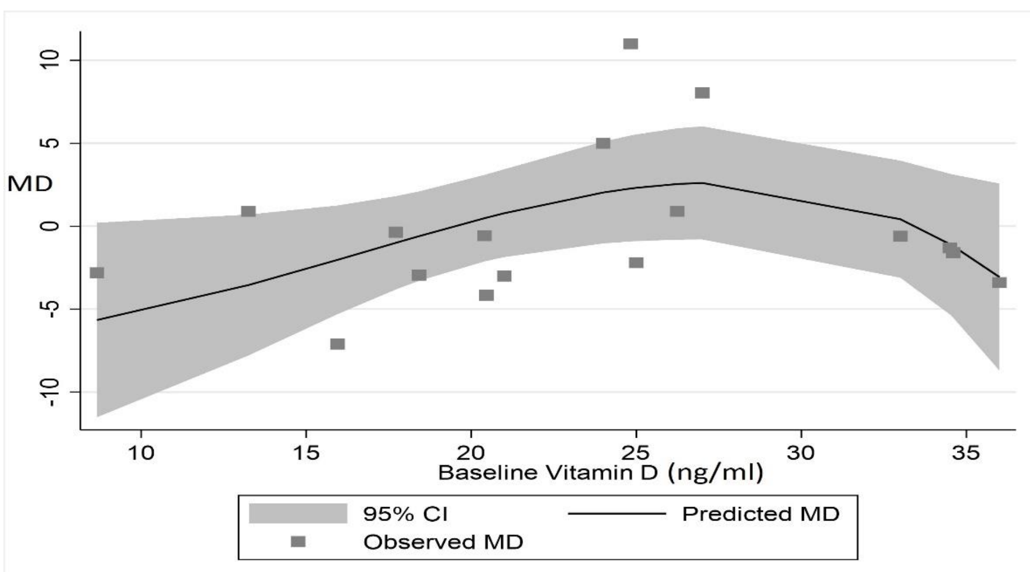


Figure S16. Non-linear meta-regression analysis revealed a significant association between P1NP level and baseline vitamin D level.

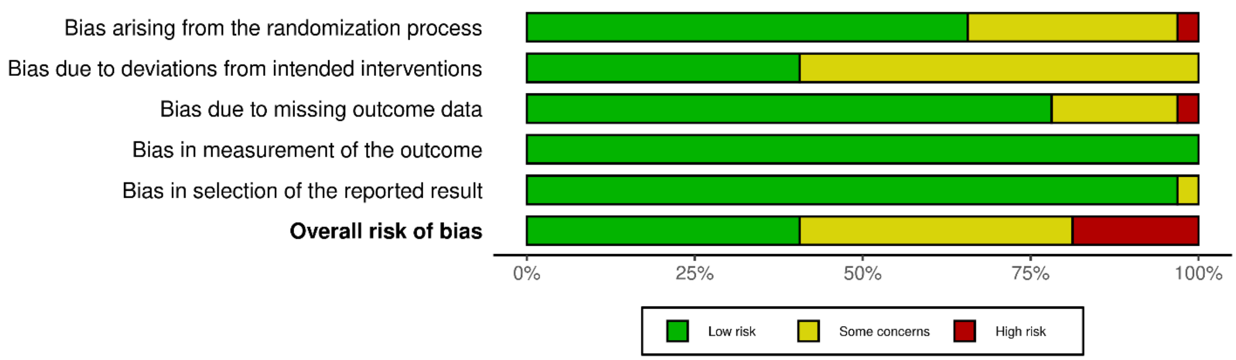


Figure S17a – A summary of risk of bias analysis showing the percentage of studies with "some concerns" or "high risk" of selection, performance, detection, attrition, reporting, or other bias.

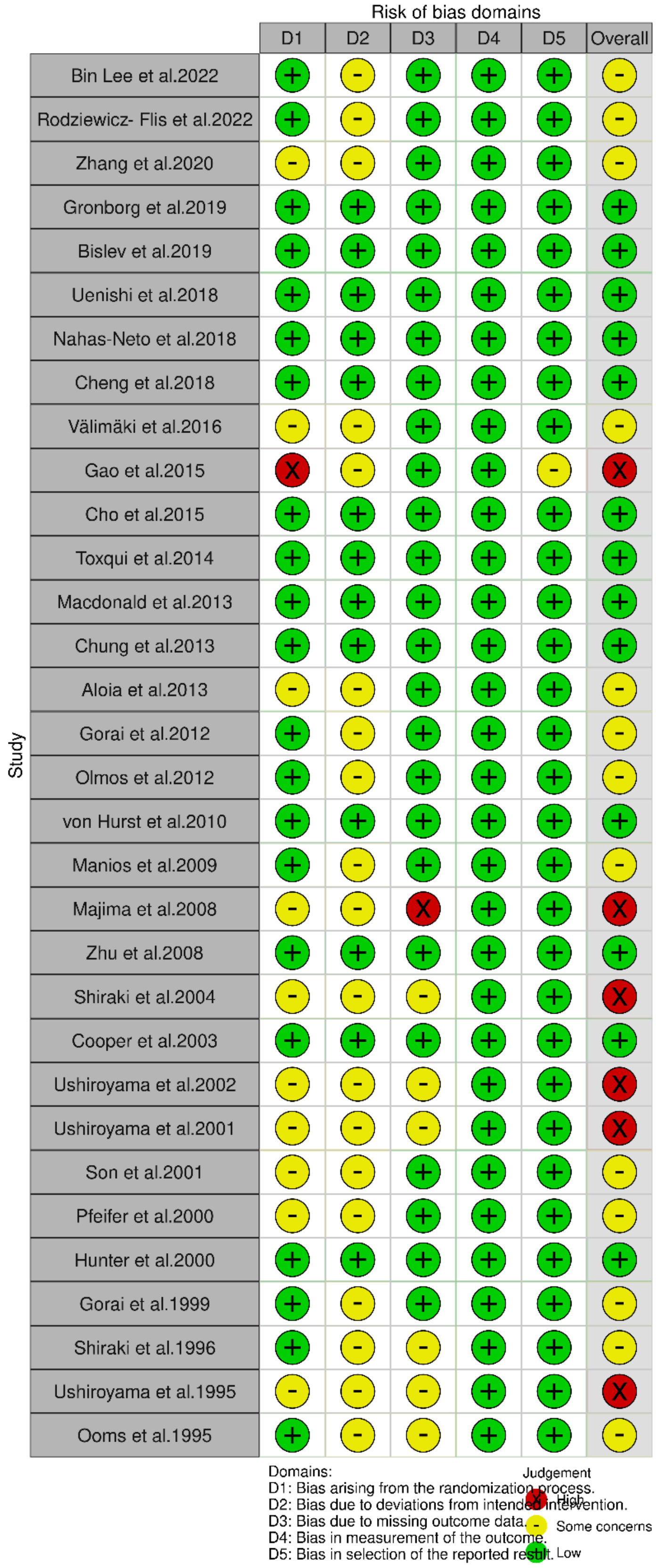


Figure S17b – Risk of bias analysis of all studies included in the meta-analysis.
(+) Circles filled in green = Low risk of bias
(-) Circles filled in yellow = Some concerns
(×) Circles filled in red = High risk of bias

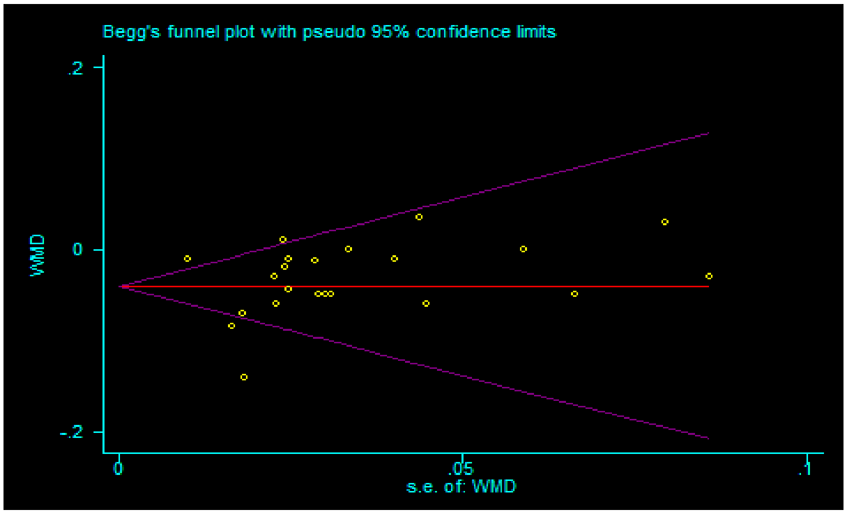


Figure S18. Funnel plot showing results of all studies testing the effects of vitamin D supplementation on sCTX.

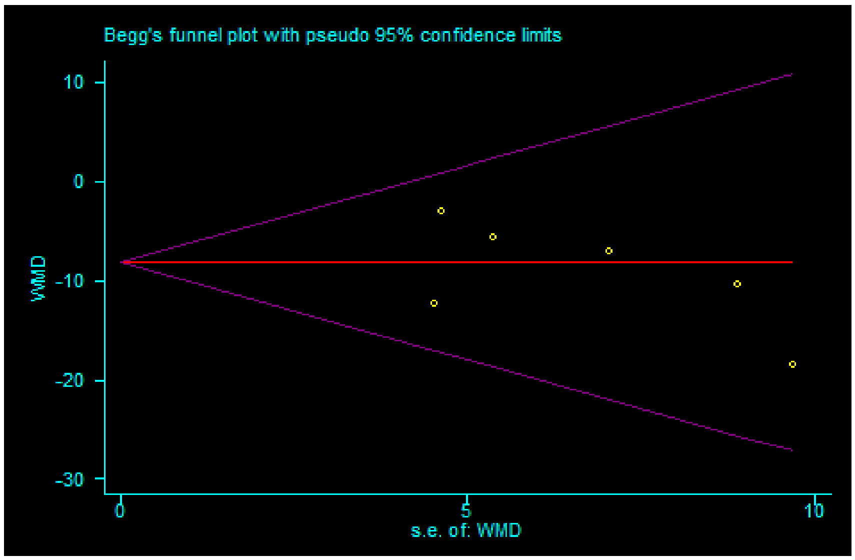


Figure S19. Funnel plot showing results of all studies testing the effects of vitamin D supplementation on uNTX.

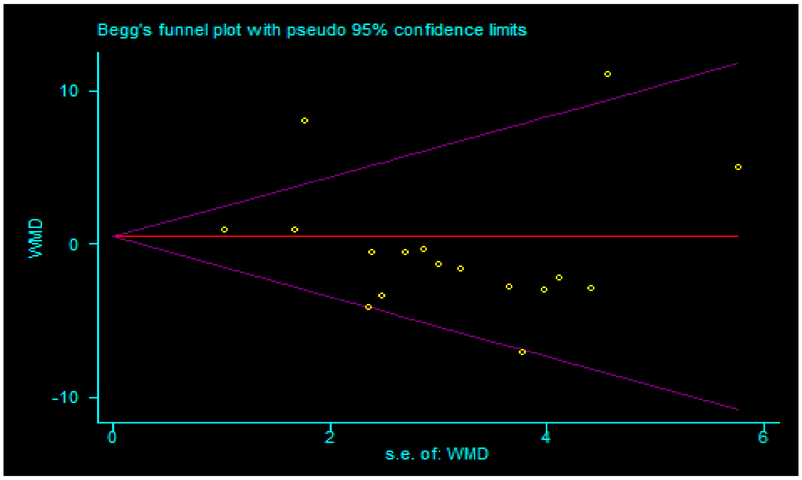


Figure S20. Funnel plot showing results of all studies testing the effects of vitamin D supplementation on OC.

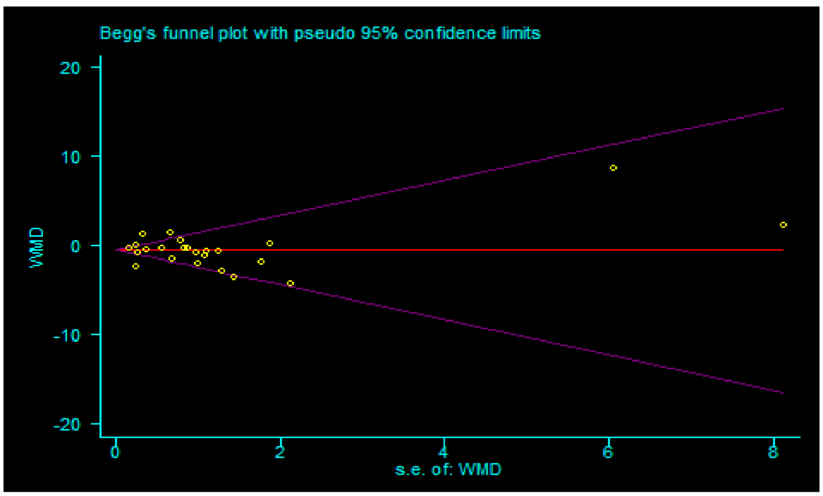


Figure S21. Funnel plot showing results of all studies testing the effects of vitamin D supplementation on P1NP.

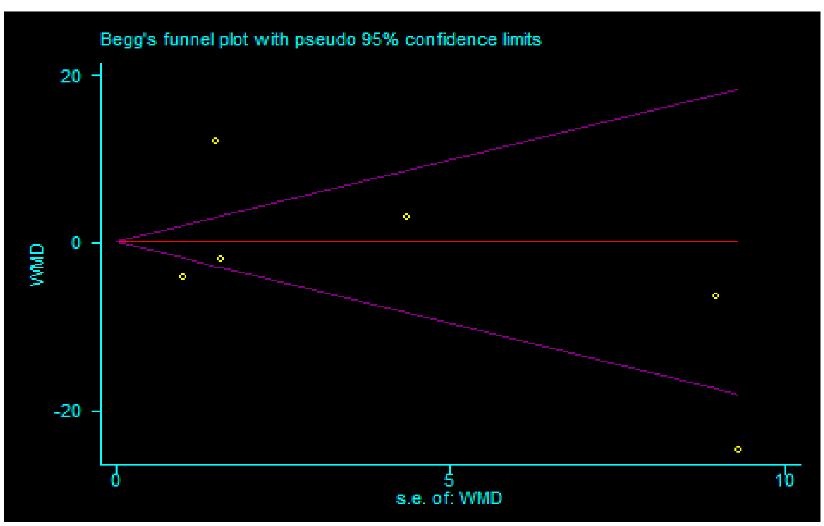


Figure S22. Funnel plot showing results of all studies testing the effects of vitamin D supplementation on BALP.