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Supplementary Material: *Reproduction, Fertility and Development*

Supplementary Material

Changes in bone turnover and calcium homeostasis during pregnancy and lactation in mammals: a meta-analysis

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Data S1. Search keywords.

KEYWORD USED IN PUBMED
#1 ("bone remodeling"[MeSH Terms] OR "bone and bones"[MeSH Terms] OR "bone density"[MeSH Terms] OR "Skeleton"[MeSH Terms] OR "bone remodeling"[TIAB] OR "bone and bones"[TIAB] OR "bone density"[TIAB] OR "Skeleton"[TIAB] OR "Bone turnover"[TIAB] OR "Bone Mineral content"[TIAB] OR "Bone Loss"[TIAB])
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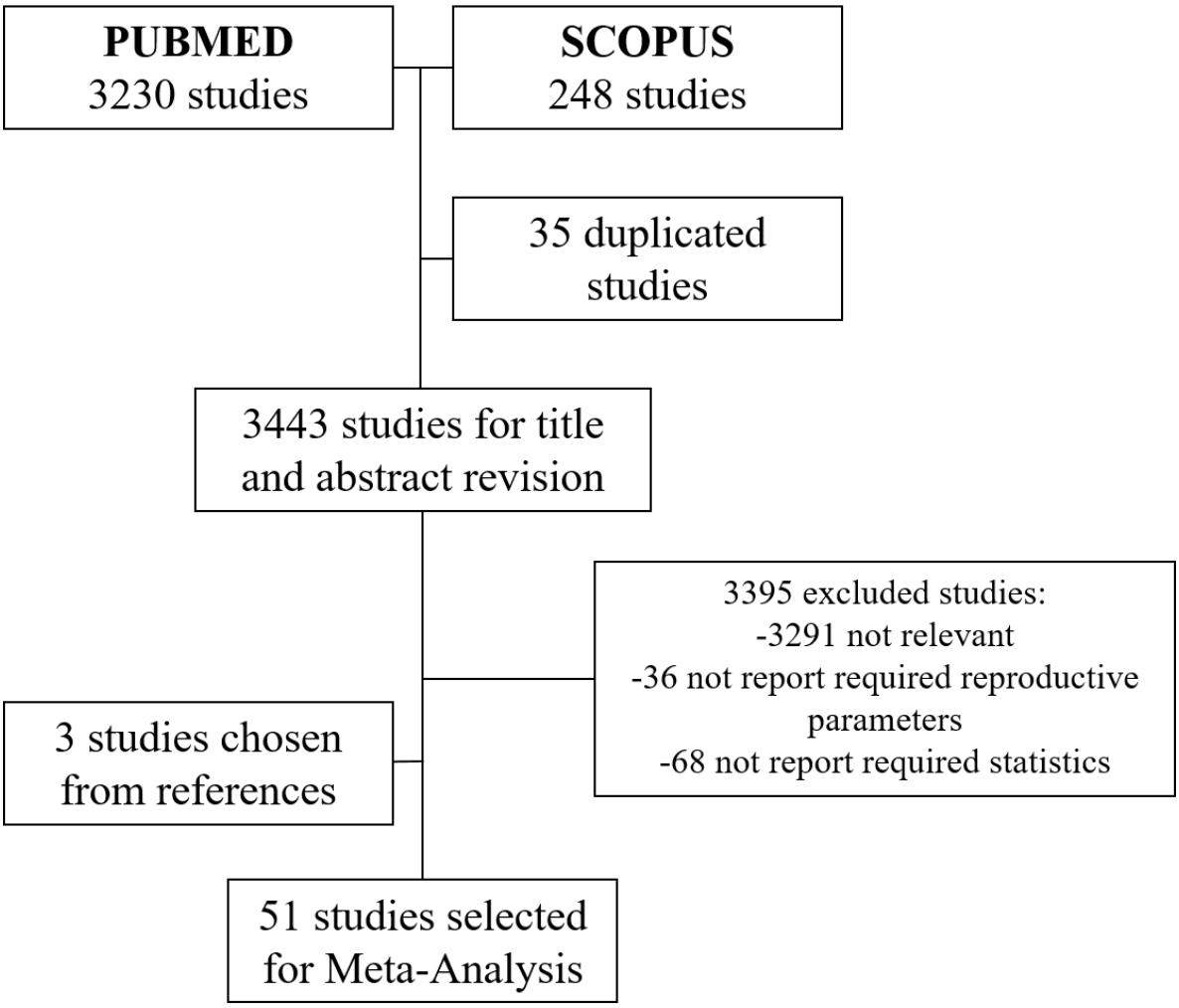
KEYWORDS USED IN SCOPUS

(TITLE-ABS-KEY(“Reproduction”) OR TITLE-ABS-KEY(“Lactation”) OR TITLE-ABS-KEY(“Pregnancy”)) AND (TITLE-ABS-KEY(“bone remodeling”) OR TITLE-ABS-KEY(“bone”) OR TITLE-ABS-KEY(“bone density”) OR TITLE-ABS-KEY(“Skeleton”)) AND (TITLE-ABS-KEY(“mammals”))

Data S2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) illustrating the process of study selection.



Data S3. Calcium effect sizes in relation to control.

	Species	n effect size	SMD	Lower CI	Upper CI	p-value
Early Pregnancy	Human	5	-0.488	-1.617	0.64	0.396
	Rat	1	0	-1.048	1.048	
	Pig	4	-0.474	-1.243	0.295	0.227
	Total	10	-0.434	-1.041	0.174	0.162
Mid Pregnancy	Human	7	-1.144	-2.003	-0.285	0.009
	Southern pig-tailed macaque	1	-1.055	-1.572	-0.537	
	Pig	3	-0.049	-0.851	0.754	0.906
	Guinea Pig	1	0.283	-0.139	0.706	
	Total	12	-0.695	-1.202	-0.188	0.007
Late Pregnancy	Cow	1	-0.397	-1.054	0.259	
	Guinea Pig	1	-0.662	-1.091	-0.232	
	Human	6	-1.013	-1.489	-0.536	< 0.001
	Crab-eating macaque	2	-0.872	-1.994	0.249	0.127
	Mice	2	-0.084	-1.126	0.958	0.875
	Rat	3	-1.475	-2.293	-0.657	< 0.001
	Pig	4	-0.74	-1.037	-0.443	< 0.001
	Total	19	-0.808	-1.022	-0.594	< 0.001
Pregnancy	**Total**	**41**	**-0.704**	**-0.956**	**-0.452**	**< 0.001**
Early Lactation	Dog	1	-0.312	-1.706	1.083	
	Guinea Pig	1	-0.374	-0.795	0.048	
	Human	5	0.224	-0.374	0.822	0.463
	Crab-eating macaque	1	0.074	-0.554	0.702	
	Pig	9	-1.188	-1.678	-0.698	< 0.001
	Total	17	-0.596	-0.972	-0.22	0.002
Mid Lactation	Dog	1	-1.123	-2.614	0.368	
	Guinea Pig	1	-0.063	-1.077	0.952	
	Human	2	-0.312	-3.353	2.729	0.841
	Crab-eating macaque	2	0.444	-0.559	1.448	0.386
	Rat	2	-1.318	-2.201	-0.435	0.003
	Mice	1	1.456	0.486	2.425	
	Pig	1	-1.206	-1.898	-0.513	
	Total	10	-0.277	-1.042	0.488	0.477
Late Lactation	Guinea Pig	1	-0.680	-1.723	0.363	
	Human	1	0.216	-0.405	0.838	
	Mice	2	0	-0.806	0.806	1
	Crab-eating macaque	2	-0.315	-2.245	1.616	0.749
	Southern pig-tailed macaque	1	-0.417	-0.937	0.104	
	Rat	4	0.182	-0.957	1.322	0.754
	Total	11	-0.086	-0.527	0.355	0.701
Lactation	**Total**	**38**	**-0.374**	**-0.655**	**-0.092**	**0.009**

Data S4. Calcium effect sizes in relation to late pregnancy.

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Rat	1	3.139	1.574	4.704	
	Dog	1	0.354	-0.633	1.342	
	Deer	1	-1.898	-3.567	-0.229	
	Pig	3	0.604	0.085	1.124	0.023
	Human	5	0.857	0.11	1.604	0.025
	Total	11	0.701	0.189	1.214	0.007
Mid Pregnancy	Dog	1	0.222	-0.761	1.205	
	Deer	1	0	-1.386	1.386	
	Guinea Pig	1	1.503	1.027	1.979	
	Pig	3	0.738	0.034	1.443	0.04
	Human	6	-0.29	-1.152	0.573	0.51
	Total	12	0.219	-0.303	0.742	0.411
Pregnancy	**Total**	**23**	**0.448**	**0.087**	**0.809**	**0.015**
Early Lactation	Dog	1	-0.111	-1.092	0.87	
	Deer	1	3.195	1.104	5.285	
	Guinea Pig	1	0.189	-0.23	0.608	
	Crab-eating macaque	1	1.348	0.643	2.052	
	Bufalo	3	0.841	-0.384	2.067	0.178
	Goat	3	1.278	0.56	1.996	< 0.001
	Human	4	0.682	-0.148	1.513	0.107
	Sheep	7	0.504	-0.051	1.059	0.075
	Pig	8	-0.317	-0.717	0.083	0.12
	Horse	8	0.005	-0.259	0.269	0.97
	Total	37	0.282	0.05	0.515	0.017
Mid Lactation	Rat	1	1.186	0.05	2.322	
	Human	1	-0.076	-0.817	0.665	
	Dog	1	0.374	-0.615	1.362	
	Sheep	1	1.13	-0.088	2.349	
	Bufalo	2	0.217	-0.406	0.841	0.495
	Horse	2	0.301	-0.226	0.827	0.263
	Crab-eating macaque	2	2.127	0.908	3.347	< 0.001
	Goat	3	0.668	-0.01	1.345	0.053
	Total	13	0.747	0.305	1.19	< 0.001
Late Lactation	Dog	1	-0.35	-1.338	0.637	
	Crab-eating macaque	2	1.498	-0.775	3.772	0.196
	Rat	2	0.6	-0.555	1.755	0.309
	Mice	3	-0.009	-0.998	0.98	0.985
	Total	8	0.492	-0.256	1.24	0.197
Lactation	**Total**	**58**	**0.42**	**0.215**	**0.625**	**< 0.001**

Data S5.

Bone mineral density effect sizes in relation to control

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Rat	4	-0.955	-1.492	-0.417	< 0.001
Mid Pregnancy	Human	3	-0.049	-0.414	0.315	0.79
Late Pregnancy	Rat	17	-0.46	-0.81	-0.109	0.01
	Human	2	-0.427	-1.054	0.2	0.182
	Cavia	1	-0.128	-1.058	0.803	
	Total	20	-0.431	-0.728	-0.133	0.005
Pregnancy	Total	27	-0.444	-0.684	-0.204	< 0.001
Early Lactation	Human	7	-0.335	-0.575	-0.095	0.006
	Rat	2	-2.816	-5.285	-0.348	0.025
	Total	9	-0.61	-1.07	-0.151	0.009
Mid Lactation	Rat	2	-1.939	-2.837	-1.04	< 0.001
	Human	2	-0.892	-1.504	-0.28	0.004
	Total	4	-1.225	-1.843	-0.608	< 0.001
Late Lactation	Human	2	-1.018	-2.13	0.095	0.073
	Rat	12	-1.374	-2.016	-0.732	< 0.001
	Total	14	-1.287	-1.81	-0.764	< 0.001
Lactation	Total	27	-1.044	-1.364	-0.724	< 0.001

Bone mineral density effect sizes in femur, tibia and lumbar vertebrae in relation to control

		n effect size	SMD	Lower IC	Upper IC	p-value
Pregnancy	Femur	6	-0.411	-1.111	0.289	0.249
	Tibia	5	-0.846	-1.592	-0.099	0.026
	Lumbar vertebrae	7	-0.37	-1.016	0.277	0.262
Lactation	Femur	5	-1.425	-2.088	-0.762	< 0.001
	Tibia	6	-1.421	-2.687	-0.155	0.028
	Lumbar spine	10	-1.087	-1.677	-0.498	< 0.001

Data S6. Parathyroid hormone effect sizes in relation to control.

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Mice	1	-0.088	-1.101	0.924	
	Human	4	-0.537	-0.971	-0.102	0.015
	Total	5	-0.467	-0.866	-0.068	0.022
Mid Pregnancy	Southern pig-tailed macaque	1	0.068	-0.427	0.563	
	Human	4	-0.822	-1.265	-0.38	< 0.001
	Total	5	-0.57	-1.08	-0.06	0.028
Late Pregnancy	Cow	1	-0.033	-0.932	0.865	
	Rat	2	0.462	-4.724	5.648	0.861
	Mice	3	-0.634	-1.238	-0.03	0.04
	Human	3	-0.242	-0.783	0.299	0.38
	Total	9	-0.261	-0.951	0.429	0.459
Pregnancy	Total	19	-0.426	-0.75	-0.101	0.01
Early Lactation	Mice	1	-1.107	-2.278	0.063	
	Cow	2	0.229	-0.41	0.869	0.482
	Human	3	-0.215	-0.704	0.273	0.388
	Total	6	-0.156	-0.525	0.212	0.406
Late Lactation	Southern pig-tailed macaque	1	-0.218	-0.735	0.299	
	Rat	2	0.454	-0.912	1.82	0.515
	Mice	2	-1.043	-1.802	-0.285	0.007
	Total	5	-0.279	-0.948	0.39	0.414
Lactation	Total	11	-0.216	-0.547	0.114	0.199

Data S7. Parathyroid hormone effect sizes in relation to late pregnancy.

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Deer	1	-2.633	-4.527	-0.740	
	Mice	1	0	-1.187	1.187	
	Human	4	-0.233	-0.656	0.19	0.28
	Total	6	-0.348	-0.824	0.129	0.152
Mid Pregnancy	Deer	1	-2.423	-4.248	-0.598	
	Dog	1	0.07	-0.91	1.05	
	Human	4	-0.524	-0.949	-0.098	0.016
	Total	6	-0.537	-0.973	-0.101	0.016
Pregnancy	Total	12	-0.389	-0.673	-0.106	0.007
Early Lactation	Mice	1	0.046	-1.044	1.137	
	Dog	1	-0.746	-1.76	0.267	
	Deer	1	-0.261	-1.652	1.131	
	Cow	2	0.293	-0.123	0.708	0.167
	Horse	2	0.082	-0.693	0.857	0.835
	Sheep	3	10.085	8.093	12.077	< 0.001
	Human	3	0.016	-0.489	0.52	0.951
	Buffalo	5	0.087	-0.306	0.48	0.663
	Total	18	0.645	0.06	1.231	0.031
Mid Lactation	Dog	1	-0.308	-1.294	0.677	
	Horse	2	0.019	-1.678	1.717	0.982
	Total	3	-0.11	-1.061	0.841	0.821
Late Lactation	Dog	1	-0.415	-1.406	0.575	
	Rat	2	-0.444	-4.135	3.248	0.814
	Mice	3	0.245	-0.421	0.912	0.471
	Total	6	-0.041	-0.976	0.895	0.932
Lactation	Total	27	0.37	-0.075	0.816	0.103

Data S8.

Calcitonin effect sizes in relation to control

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Human	1	-0.242	-1.016	0.532	
Mid Pregnancy	Human	1	-0.628	-1.418	0.161	
Late Pregnancy	Rat	1	-0.214	-1.141	0.712	
	Human	1	-0.55	-1.35	0.249	
	Total	2	-0.407	-1.012	0.198	0.188
Pregnancy	Total	4	-0.42	-0.828	-0.012	0.044
Early Lactation	Human	1	-0.187	-0.96	0.586	
Late Lactation	Rat	1	-0.02	-0.944	0.904	
Lactation	Total	2	-0.118	-0.711	0.475	0.696

Calcitonin effect sizes in relation to late pregnancy

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Dog	1	0.125	-0.856	1.106	
	Deer	1	0.261	-1.131	1.652	
	Human	1	0.273	-0.486	1.031	
	Total	3	0.224	-0.327	0.775	0.425
Mid Pregnancy	Dog	1	-0.158	-1.14	0.823	
	Deer	1	0.549	-0.862	1.961	
	Human	1	0	-0.755	0.755	
	Total	3	0.034	-0.517	0.585	0.904
Pregnancy	Total	6	0.129	-0.261	0.519	0.516
Early Lactation	Dog	1	-0.65	-1.656	0.355	
	Deer	1	2.362	0.557	4.168	
	Human	1	0.202	-0.555	0.959	
	Buffalo	5	0.888	0.475	1.301	< 0.001
	Total	8	0.68	0.194	1.167	0.006
Mid Lactation	Dog	1	0.561	-0.438	1.56	
Late Lactation	Dog	1	-0.423	-1.414	0.568	
	Rat	1	0.232	-0.695	1.159	
	Total	2	-0.074	-0.751	0.603	0.831
Lactation	Total	11	0.524	0.128	0.92	0.009

Data S9. Calcitriol effect sizes in relation to control.

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Human	3	0.032	-2.239	2.304	0.978
	Guinea Pig	1	1.558	0.503	2.612	
	Pig	1	0.427	-0.176	1.03	
	Total	5	0.401	-1.134	1.937	0.609
Mid Pregnancy	Human	3	2.46	1.306	3.615	< 0.001
	Southern pig-tailed macaque	1	0.94	0.427	1.453	
	Total	4	2.036	0.657	3.414	0.004
Late Pregnancy	Cow	1	0.199	-0.453	0.852	
	Guinea Pig	1	1.245	0.236	2.255	
	Pig	1	0.885	0.216	1.553	
	Rat	2	2.6	1.629	3.571	< 0.001
	Mice	2	2.396	1.246	3.545	< 0.001
	Human	3	3.083	0.098	6.067	0.043
	Total	10	2.149	0.732	3.566	0.003
Pregnancy	Total	19	1.659	0.63	2.689	0.002
Early Lactation	Guinea Pig	1	1.077	0.089	2.066	
	Pig	1	0.825	0.16	1.49	
	Human	3	1.648	-2.252	5.549	0.408
	Total	5	1.373	-0.888	3.635	0.234
Late Lactation	Southern pig-tailed macaque	1	-0.298	-0.816	0.22	
	Rat	2	4.16	-2.315	10.636	0.208
	Total	3	1.869	-0.402	4.14	0.107
Lactation	Total	8	1.634	-0.007	3.274	0.051

Data S10. Calcitriol effect sizes in relation to late pregnancy.

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Sheep	1	-7.033	-9.177	-4.888	
	Goat	1	-1.215	-2.086	-0.345	
	Guinea Pig	1	0.015	-0.909	0.939	
	Pig	1	-0.86	-1.567	-0.153	
	Human	3	-2.22	-4.51	0.071	0.058
	Total	7	-2.084	-3.442	-0.725	0.003
Mid Pregnancy	Sheep	2	-3.388	-7.265	0.488	0.087
	Goat	2	-0.329	-1.128	0.47	0.42
	Human	3	-1.004	-2.348	0.34	0.143
	Total	7	-1.35	-2.309	-0.39	0.006
Pregnancy	Total	14	-1.7	-2.49	-0.91	< 0.001
Early Lactation	Guinea Pig	1	-0.535	-1.476	0.405	
	Pig	1	-0.036	-0.751	0.68	
	Human	3	-1.319	-2.526	-0.112	0.032
	Sheep	4	-2.426	-2.99	-1.863	< 0.001
	Goat	4	1.685	0.53	2.84	0.004
	Total	13	-0.592	-1.498	0.314	0.2
Mid Lactation	Sheep	3	-2.538	-3.07	-2.005	< 0.001
	Goat	2	2.893	2.083	3.702	< 0.001
	Total	5	-0.11	-2.413	2.193	0.926
Late Lactation	Goat	1	1.978	1.002	2.955	
	Rat	1	-1.306	-2.329	-0.283	
	Total	2	0.34	-2.879	3.558	0.836
Lactation	Total	20	-0.382	-1.189	0.424	0.353

Data S11. Osteocalcin effect sizes in relation to control.

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Sheep	1	-4.083	-5.027	-3.139	
	Rat	1	0.589	-0.412	1.59	
	Mice	1	-0.263	-1.315	0.789	
	Pig	1	0.093	-0.59	0.776	
	Human	4	-1.119	-2.038	-0.199	0.017
	Total	8	-1.043	-2.028	-0.057	0.038
Mid Pregnancy	Guinea Pig	1	-3.064	-4.557	-1.57	
	Southern pig-tailed macaque	1	-2.059	-2.635	-1.482	
	Human	4	-1.49	-2.426	-0.553	0.002
	Total	6	-1.79	-2.559	-1.022	< 0.001
Late Pregnancy	Pig	1	-0.285	-0.983	0.412	
	Guinea Pig	1	-2.849	-4.288	-1.411	
	Rat	3	-0.591	-3.333	2.152	0.673
	Mice	3	-0.871	-1.59	-0.152	0.018
	Human	4	-0.6	-1.35	0.149	0.117
	Total	12	-0.839	-1.647	-0.03	0.042
Pregnancy	Total	26	-1.109	-1.576	-0.642	< 0.001
Early Lactation	Sheep	1	-1.049	-1.961	-0.137	
	Rat	1	0.97	-0.066	2.005	
	Pig	2	-1.165	-1.692	-0.637	< 0.001
	Human	4	0.498	-0.047	1.044	0.073
	Total	8	-0.087	-0.781	0.607	0.806
Mid Lactation	Human	1	0.342	-0.253	0.937	
	Mice	1	1.968	0.667	3.269	
	Total	2	1.048	-0.531	2.627	0.193
Late Lactation	Cow	1	-1.684	-2.426	-0.942	
	Southern pig-tailed macaque	1	1.249	0.695	1.804	
	Human	1	0.024	-0.567	0.615	
	Rat	1	1.089	0.039	2.139	
	Mice	2	-0.536	-2.552	1.481	0.603
	Total	6	-0.044	-1.089	1.002	0.935
Lactation	Total	16	0.069	-0.448	0.587	0.793

Data S12. Osteocalcin effect sizes in relation to late pregnancy.

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Goat	1	0.57	-0.246	1.386	
	Sheep	1	1.843	0.888	2.798	
	Mice	1	0.714	-0.411	1.838	
	Rat	1	0.258	-0.726	1.242	
	Pig	1	0.395	-0.317	1.106	
	Human	4	-0.409	-0.945	0.126	0.134
	Total	9	0.194	-0.326	0.714	0.465
Mid Pregnancy	Guinea Pig	1	0.1	-0.948	1.148	
	Goat	3	0.834	0.351	1.318	< 0.001
	Sheep	3	0.812	0.33	1.295	< 0.001
	Human	4	-0.727	-1.097	-0.358	< 0.001
	Total	11	0.173	-0.321	0.667	0.493
Pregnancy	Total	20	0.182	-0.167	0.53	0.307
Early Lactation	Buffalo	5	1.378	0.546	2.21	0.001
	Goat	14	0.632	0.148	1.116	0.01
	Horse	10	0.218	-0.031	0.467	0.086
	Human	4	1.015	0.634	1.396	< 0.001
	Sheep	16	-0.686	-1.498	0.127	0.098
	Rat	1	0.393	-0.596	1.383	
	Pig	2	-0.734	-1.254	-0.214	0.006
	Total	52	0.333	0.045	0.62	0.023
Mid Lactation	Goat	6	0.28	-0.763	1.323	0.598
	Horse	4	-0.065	-0.5	0.371	0.771
	Human	1	0.193	-0.399	0.785	
	Shep	4	0.592	-0.893	2.077	0.435
	Total	15	0.244	-0.281	0.769	0.362
Late Lactation	Goat	1	0.221	-0.582	1.023	
	Human	1	-0.135	-0.726	0.457	
	Rat	1	0.572	-0.428	1.571	
	Mice	2	0.235	-0.999	1.47	0.709
	Total	5	0.121	-0.267	0.509	0.54
Lactation	Total	72	0.309	0.074	0.544	0.01

Data S13. Alkaline phosphatase effect sizes in relation to control.

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Rat	1	1.701	0.558	2.845	
	Human	3	-0.228	-1.461	1.005	0.717
	Total	4	0.224	-1.073	1.521	0.735
Mid Pregnancy	Human	3	0.879	-0.065	1.823	0.068
	Guinea Pig	1	-0.136	-0.56	0.287	
	Total	4	0.544	-0.09	1.178	0.093
Late Pregnancy	Guinea Pig	1	-0.14	-0.439	0.159	
	Cow	1	0.186	-0.466	0.838	
	Crab-eating Macaque	2	-1.011	-1.564	-0.457	< 0.001
	Rat	2	0.017	-3.435	3.47	0.992
	Human	3	1.949	1.025	2.873	< 0.001
	Total	9	0.487	-0.323	1.297	0.238
Pregnancy	Total	17	0.454	-0.07	0.978	0.089
Early Lactation	Human	2	1.565	0.203	2.927	0.024
	Guinea Pig	1	-2.144	-2.674	-1.613	
	Crab-eating Macaque	1	-0.272	-0.903	0.359	
	Rat	1	1.398	0.305	2.491	
	Total	5	0.415	-1.128	1.959	0.598
Mid Lactation	Dog	1	1.422	-0.129	2.973	
	Human	1	3.914	2.418	5.411	
	Crab-eating Macaque	3	0.245	-0.27	0.759	0.352
	Total	5	1.159	0.006	2.313	0.049
Late Lactation	Dog	1	3.347	1.2	5.495	
	Crab-eating Macaque	1	0.552	-0.419	1.524	
	Rat	2	2.048	1.164	2.931	< 0.001
	Total	4	1.787	0.71	2.865	0.001
Lactation	Total	14	1.078	0.252	1.904	0.011

Data S14. Alkaline phosphatase effect sizes in relation to late pregnancy.

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Rat	1	-0.125	-1.106	0.856	
	Human	3	-2.318	-2.764	-1.873	< 0.001
	Deer	1	-1.838	-3.491	-0.186	
	Total	5	-1.815	-2.714	-0.915	< 0.001
Mid Pregnancy	Human	3	-1.654	-2.639	-0.67	< 0.001
	Guinea Pig	1	-0.181	-0.605	0.243	
	Deer	1	-1.224	-2.735	0.286	
	Total	5	-1.235	-2.029	-0.441	0.002
Pregnancy	Total	10	-1.526	-2.185	-0.866	< 0.001
Early Lactation	Deer	1	-1.851	-3.507	-0.195	
	Guinea Pig	1	-2.77	-3.362	-2.178	
	Crab-eating Macaque	1	0.82	0.158	1.482	
	Rat	1	-0.529	-1.526	0.468	
	Buffalo	5	4.081	3.133	5.029	< 0.001
	Human	2	-0.52	-0.983	-0.058	0.027
	Total	11	1.333	-0.059	2.725	0.06
Mid Lactation	Human	1	-0.925	-1.848	-0.003	
	Crab-eating Macaque	3	1.267	0.837	1.697	< 0.001
	Total	4	0.753	-0.206	1.712	0.124
Late Lactation	Crab-eating Macaque	1	1.235	0.453	2.017	
	Rat	2	1.22	-1.633	4.073	0.402
	Total	3	1.176	-0.255	2.607	0.107
Lactation	Total	18	1.14	0.26	2.02	0.011

Data S15.

Bone-specific alkaline phosphatase effect sizes in relation to control

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Human	3	-0.249	-0.736	0.237	0.315
Mid Pregnancy	Human	3	0.144	-0.678	0.967	0.731
Late Pregnancy	Cow	1	-6.154	-7.975	-4.333	
	Human	3	1.657	-0.161	3.475	0.074
	Total	4	-0.097	-2.88	2.686	0.946
Pregnancy	Total	10	-0.015	-0.892	0.862	0.973
Early Lactation	Cow	2	-6.564	-7.938	-5.189	< 0.001
	Human	2	2.22	0.521	3.919	0.01
	Total	4	-2.066	-6.605	2.473	0.372
Mid Lactation	Human	1	0.495	-0.395	1.385	
Lactation	Total	5	-0.43	-1.402	0.542	0.386

Bone-specific alkaline phosphatase effect sizes in relation to late pregnancy

	Species	n effect size	SMD	Lower IC	Upper IC	p-value
Early Pregnancy	Human	3	-1.983	-3.801	-0.165	0.033
Mid Pregnancy	Goat	2	2.587	0.612	4.562	0.01
	Sheep	2	0.82	0.23	1.41	0.006
	Human	3	-1.707	-3.251	-0.163	0.03
	Total	7	0.226	-1.104	1.557	0.739
Pregnancy	Total	10	-0.434	-1.546	0.678	0.444
Early Lactation	Goat	10	-0.391	-0.88	0.099	0.118
	Sheep	11	-0.35	-1.203	0.503	0.421
	Cow	2	-6.564	-7.938	-5.189	< 0.001
	Human	2	-0.297	-2.45	1.856	0.787
	Total	25	-0.726	-1.276	-0.176	0.01
Mid Lactation	Sheep	4	0.264	-0.715	1.244	0.597
	Goat	4	-0.438	-1.442	0.567	0.393
	Human	1	-0.145	-1.023	0.732	
	Total	9	-0.088	-0.695	0.518	0.775
Late Lactation	Goat	1	-0.131	-0.932	0.67	
Lactation	Total	35	-0.526	-0.942	-0.109	0.013

Data S16. Sixty **s**tudies selected for meta-analysis: 51 studies from literature search and 9 women studies chosen by authors.

Ardawi, M.S.M., Nasrat, H.A., and BA'Aqueel, H.S. (1997). Calcium-regulating hormones and parathyroid hormone-related peptide in normal human pregnancy and postpartum: a longitudinal study. *Eu. J. Endocrinol*. **137**, 402–409.

Ardeshirpour L., Dann, P., Adams, D.J., Nelson, T., VanHouten, J., Horowitz, M.C., and Wysolmerski, J.J. (2007). Weaning triggers a decrease in Receptor Activator of Nuclear Factor-κB Ligand Expression, Widespread Osteoclast Apoptosis, and Rapid Recovery of Bone Mass after Lactation in Mice. *Endocrinology*. **148**, 3875–3886.

Black, A.J., Topping, J., Durham, B., Farquharson, R.G., and Fraser, W.D. (2000). A detailed assessment of alterations in bone turnover, calcium homeostasis, and bone density in normal pregnancy. *J. Bone Miner. Res*. ***15***, 557–563.

Bowman, B.M., Siska, C.C., Miller, S.C. (2002). Greatly increased cancellous bone formation with rapid improvements in bone structure in the rat maternal skeleton after lactation. *J. Bone Miner. Res*. **17**, 1954–1960.

Brommage, R., Baxter, D.C. (1990). Inhibition of bone mineral loss during lactation by Cl2MBP. *Calcif. Tissue Int*. **47**, 69–172.

Chao, C.C., Brown, R.D., Deftos, L.J. (1985). Metabolism of calcium and phosphorus during pregnancy and lactation in white-tailed deer. *Acta Endocrinol*. **109**, 269–275.

Ciaramella, P., Piantedosi, D., De Luna, R., Oliva, G., Consalvo, F., and Persechino, A. (2000). Biochemical indicators of bone metabolic activity in buffalo (*Bubalus bubalis*) during late pregnancy and early lactation. *J. Vet. Med. A Physiol. Pathol. Clin. Med*. **47**, 431–437.

Clarke, M.V., Russell, P.K., Findlay, D.M., Sastra, S., Anderson, P.H., Skinner, J.P., Atkins, G.J., Zajac, J.D., and Davey, R.A. (2015). A role for the calcitonin receptor to limit bone loss during lactation in female mice by inhibiting osteocytic osteolysis. *Endocrinology*. **156**, 3203–3214.

Cross, N.A., Hillman, L.S., Allen, S.H., Krause, G.F., Vieira, N.E. (1995). Calcium homeostasis and bone metabolism during pregnancy, lactation, and postweaning: a longitudinal study. *Am. J. Clin. Nutr*. **61**, 514–523.

Davicco, M.J., Faulconnier, Y., Coxam, V., Dubroeucq, H., Martin-Rosset, W., and Barlet, J.P. 1994. Systemic bone growth factors in light breed mares and their foals. *Arch. Int. de Physiol. Biochim*. **102,** 115–119.

Espino, L., Guerrero, F., Suarez, M.L., Santamarina, G., Goicoa, A., and Fidalgo, L.E. (2003). Long-term effects of dietary anion-cation balance on acid-base status and bone morphology in reproducing ewes *J. Vet. Med. A Physiol. Pathol. Clin. Med*. **50**, 488–495.

Farrugia, W., Fortune, C.L., Heath, J., Caple, I.W., and Wark, J.D. (1989). Osteocalcin as an index of osteoblast function during and after ovine pregnancy. *Endocrinology*. **125**, 1705–1710.

Filipović, N., Stojević, Z., Prvanović, N., and Tuček, Z. (2014). The influence of late pregnancy and lactation on bone metabolism in mares. *Res. Vet. Sci*. **97**, 194–198.

Filipovic, N., Stojevic, Z., Zdelar-Tuk, M., and Kusec, V. (2008). Plasma parathyroid hormone-related peptide and bone metabolism in periparturient dairy cows. *Acta Vet. Hung*. **56**, 235–244.

Fudge, N.J., and Kovacs, C. (2010). Pregnancy up-regulates intestinal calcium absorption and skeletal mineralization independently of the vitamin D receptor. *Endocrinology*. **151**, 886–895.

Fukuda, S., and Lida, H. (1993). Histomorphometric changes in iliac trabecular bone during pregnancy and lactation in Beagle dogs. *J. Vet. Med. Sci*. **55**, 569.

Girard, C.L., Robert, S., Matte, J.J., Farmer, C., Martineau, G.P. (1996). Serum concentrations of micronutrients, packed cell volume, and blood hemoglobin during the first two gestations and lactations of sows. *Can. J. Vet. Res*. **60**, 179–185.

Gonen, E., Sahin, I., Ozbeck, M., Kovalak, E., Yologlu, S., and Ates, Y. (2005). Effects of Pregnancy and lactation on bone mineral density and their relation to the serum calcium,

phosphorus, calcitonin and parathyroid hormone levels in rats. *J. Endocrinol. Invest*. **4**, 322–326.

Gruber, H.E., and Stover, S.J. (1994). Maternal and weanling bone: the influence of lowered calcium intake and maternal dietary history. *Bone*. **15**, 167–176.

Honda, A., Kurabayashi, T., Yahata, T., Tomita, M., Matsushita, H., Takakuwa, K., and Tanaka, K. (2000). Effects of pregnancy and lactation on trabecular bone and marrow adipocytes in rats. *Calcif. Tissue Int*. **67**, 367–372.

Ichikawa, F., Katagiri, K., Higuchi, Y., Takeda, S., and Saito, K. (2000). 1α-Hydroxyvitamin D 3 prevents the decrease of bone mineral density in lactating Beagles. *J. Vet. Med. Sci*. **62**, 75-79.

Kirby, B.J., Ma, Y., Martin, H.M., Favaro, K.L.B., Karaplis, A.C., and Kovacs, C.S. (2011). Skeletal recovery after weaning does not require PTHrP. J. *Bone Miner. Res*. **26**, 1242–1251.

Kirby, B.J., Ma, Y., Martin, H.M., Favaro, K.L.B., Karaplis, A.C., and Kovacs, C.S. (2013). Upregulation of calcitriol during pregnancy and skeletal recovery after lactation do not require parathyroid hormone. *J. Bone Miner. Res*. **28**, 1987–2000.

Lappeteläinen, R., Lappeteläinen, E., Hassinen, T., and Hahl, M. 1993. Biochemical indicators of bone metabolic activity in bovine periparturient hypocalcemia. J. Vet. Med. **40**, 67–72.

Lees, C.J., and Jerome, C.P. (1998). Effects of pregnancy and lactation on bone in cynomolgus macaques: Histomorphometric analysis of iliac biopsies. *Bone*. **22**, 545–549.

Lees, C.J., Jerome, C.P., Register, T.C., and Carlson, C.S. (1998). Changes in bone mass and bone biomarkers of cynomolgus monkeys during pregnancy and lactation. *J. Clin. Endocrinol. Metab*. **83**, 4298–4302.

Liesegang, A., Loch, L., Bürgi, E., and Risteli, J. (2005). Influence of phytase added to a vegetarian diet on bone metabolism in pregnant and lactating sows. *J. Anim. Physiol. Anim. Nutr*. **89**, 120–128.

Liesegang, A., Risteli, J., and Wanner, M. (2006). The effects of first gestation and lactation on bone metabolism in dairy goats and milk sheep. *Bone*. **38**, 794–802.

Liesegang A, Risteli J, Wanner M. (2007). Bone metabolism of milk goats and sheep during second pregnancy and lactation in comparison to first lactation. *J. Anim. Physiol. Anim. Nutr*. **91**, 217–225.

Liesegang, A. (2008.) Influence of anionic salts on bone metabolism in periparturient dairy goats and sheep. *J. Dairy Sci*. **91**, 2449–2460.

Liu, X.S., Ardeshirpour, L., Vanhouten, J.N., Shane, E., and Wysolmerski, J.J. (2012). Site-specific changes in bone microarchitecture, mineralization, and stiffness during lactation and after weaning in mice. *J. Bone Min. Res*. **27**, 865–875.

Lozupone, E., and Favia, A. (1988). Distribution of resorption processes in the compacta and spongiosa of bones from lactating rats fed a low-calcium diet. *Bone*. **9**, 215–224.

Miller, M.A., Omura, T.H., and Miller, S.C. (1989). Increased cancellous bone remodeling during lactation in beagles. *Bone*. **10**, 279–85.

Miller, S.C., and Bowman, B.M. (2004). Rapid improvements in cortical bone dynamics and structure after lactation in established breeder rats. *Anat. Rec. A Discov. Mol. Cell. Evol. Biol.* **276**, 143–149.

Miller, S., Shupe, J., Redd, E., Miller, M., and Omura, T. (1986). Changes in bone mineral and bone formation rates during pregnancy and lactation in rats. *Bone*. **7**, 283–287.

More, C., Bettembuk, P., Bhattoa, H.P., and Balogh, A. (2001). The effects of pregnancy and lactation on bone mineral density. *Osteoporos. Int*. **12**, 732–737.

More, C., Bhattoa, H.P., Bettembuk, P., and Balogh, A. (2003). The effects of pregnancy and lactation on hormonal status and biochemical markers of bone turnover. *Eur. J. Obstet. Gynecol. Reprod. Biol*. **106**, 209–213.

Nishiwaki, M., Yasumizu, T., Hoshi, K., and Ushijima, H. (1999). Effect of pregnancy, lactation and weaning on bone mineral density in rats as determined by dual-energy X-ray absorptiometry. *Endocr. J*. **46**, 711–716.

Ott, S.M., Lipkin, E.W., and Newell-Morris, L. (1999). Bone physiology during pregnancy and lactation in young macaques. *J. Bone Miner. Res*. **14**, 1779–1788.

Paoletti, A.M., Orrù, M., Floris, L., Guerriero, S., Ajossa, S., Romagnino, S., and Melis, G.B. (2003). Pattern of bone markers during pregnancy and their changes after delivery. *Horm. Res*. **59**, 21–29.

Purdie, D., Aaron, J., and Selby, P. (1988). Bone histology and mineral homeostasis in human pregnancy. *Br. J. Obstet. Gynaecol*. **95**, 849–54.

Qing, H., Ardeshirpour, L., Pajevic, P.D., Dusevich, V., Jahn, K., Kato, S., Wysolmerski, J.J., and Bonewald, L. (2012). Demonstration of osteocytic perilacunar/canalicular remodeling in mice during lactation. *J. Bone Min. Res*. **27**, 1018–1029.

Radojkovic, D., Pesic, M., Ristic, T. (2014). Bone turnover markers in medicamentous and physiological hyperprolactinemia in female rats. *Vojnosanit. Preg*. **71**, 559–564.

Ritchie, L.D., Fung, E.B., Halloran, B.P., Turnlund, J.R., Van Loan, M.D., Cann, C.E., and King, J.C. (1998). A longitudinal study of calcium homeostasis during human pregnancy and lactation and after resumption of menses. *Am. J. Clin. Nutr*. **67**, 693–701.

Rummens, K., van Bree, R., Van Herck, E., Zaman, Z., Bouillon, R., Van Assche, F.A., and Verhaeghe, J. (2002). Vitamin D deficiency in guinea pigs: Exacerbation of bone phenotype during pregnancy and disturbed fetal mineralization, with recovery by 1,25(OH)2D3 infusion or dietary calcium-phosphate supplementation. *Calcif. Tissue Int*. **71**, 364–375.

Sengupta, S., Arshad, M., Sharma, S., Dubey, M., and Singh, M.M. (2005). Attainment of peak bone mass and bone turnover rate in relation to estrous cycle, pregnancy and lactation in colony-bred Sprague-Dawley rats: Suitability for studies on pathophysiology of bone and therapeutic measures for its management. *J. Steroid Biochem. Mol. Biol*. **94**, 421–429.

Shahtaheri, S.M., Aaron, J.E., Johnson, D.R., and Paxton, S.K. (1999). The impact of mammalian reproduction on cancellous bone architecture. *J. Anat*. **194**, 407–21.

Shankar, K., Hidestrand, M., Haley, R., Skinner, R.A, Hogue, W., Jo, C., Simpson, P., Lumpkin, C.K., Aronson, J., Badger, T.M., and Ronis, M.J.J. (2006). Different molecular

mechanisms underlie ethanol-induced bone loss in cycling and pregnant rats. *Endocrinology*. **147**, 166–178.

Tabatabaei, N., Rodd, C.J., Kremer, R., Khavandgar, Z., Murshed, M., and Weiler, H.A. (2014). Dietary Vitamin D during pregnancy has dose-dependent effects on long bone density and architecture in guinea pig offspring but not the sows. *J. Nutr*. **25**, 1985–1994.

Tojo, Y., Kurabayashi, T., Honda, A., Yamamoto, Y., Yahata, T., Takakuwa, K., Tanaka, K. (1998). Bone structural and metabolic changes at the end of pregnancy and lactation in rats. *Am. J. Obstet. Gynecol*. **178**, 180–185.

Ulrich, U., Miller, P.B., Eyre, D.R., Chesnut, C.H., Schlebusch, H., and Soules, M.R. (2003). Bone remodeling and bone mineral density during pregnancy. Arch. Gynecol. Obstet. **268**, 309–316.

Vajda, E.G., Bowman, B.M., and Miller, S.C. (2001). Cancellous and cortical bone mechanical properties and tissue dynamics during pregnancy, lactation, and postlactation in the rat. *Biol. Reprod*. **65**, 689–95.

Vajda, E.G., Kneissel, M., Muggenburg, B., and Miller, S.C. (1999). Increased intracortical bone remodeling during lactation in Beagle dogs. *Biol. Reprod*. **61**, 1439–1444.

Verhaeghe, J., Allewaert, K., van Herck, E., Van Bree, R., Van Assche, F.A., and Bouillon, R. (1994). 1,25-Dihydroxyvitamin D3 and osteocalcin in maternal and fetal guinea pigs. *Bone* Miner. **26**, 261–73.

Verhaeghe, J., van Herck, E., Van Bree, R., Van Assche, F.A., and Bouillon, R. (1989). Osteocalcin during the reproductive cycle in normal and diabetic rats. *J. Endocrinol*. **120**, 143–51.

Weber, G.M., Witschi, A.K.M., Wenk, C., and Martens, H. (2014). Effects of dietary 25-hydroxycholecalciferol and cholecalciferol on blood vitamin D and mineral status, bone turnover, milk composition, and reproductive performance of sows. *J. Anim. Sci*. **92**, 899–909.

Woodrow, J.P., Sharpe, C.J., Fudge, N.J., Hoff, A.O., Gagel, R.F., and Kovacs, C.S. (2006). Calcitonin plays a critical role in regulating skeletal mineral metabolism during lactation. *Endocrinology*. **147**, 4010–4021.

Yildiz, M., and Oral, B. (2006). The effects of pregnancy and lactation on bone mineral density in fluoride-exposes rats. *Toxicol. Ind. Health*. **22**, 217–222.

Zeni, S.N., Di Gregorio, S., and Mautalen, C. (1999). Bone mass changes during pregnancy and lactation in the rat. *Bone*. **25**, 681–685.

Zeni, S., Weisstaub, A., Di Gregorio, S., De Ferrer, P.R., and De Portela, M.L. (2003). Bone mass changes in vivo during the entire reproductive cycle in rats feeding different dietary calcium and calcium/phosphorus ratio content. *Calcif. Tissue Inter*. **73**, 594–600.