Early Hormone Replacement Therapy and Long-Term Bone Health in Postmenopausal Women: A Real-World Propensity-Matched Study

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INTRODUCTION:

Hormone replacement therapy (HRT) has been shown to reduce bone loss in postmenopausal women. However, large-scale studies directly comparing long-term outcomes in real-world populations remain limited. While prior research has provided valuable insights, many studies have been constrained by small sample sizes and potential confounding. This retrospective cohort study aimed to evaluate the impact of HRT on long-term bone health outcomes using a large, propensity-matched population.

METHODS:

We conducted a retrospective cohort study using the TriNetX Research Network. Patients under the age of 60 with a documented diagnosis of menopause within the last 20 years were identified and divided into two cohorts based on whether they initiated HRT within one year of diagnosis. Patients with prior use of HRT, preexisting congenital and pathological bone malformations (e.g., osteoporosis, osteonecrosis, osteogenesis imperfecta, Paget's disease, etc.), and previous fractures were excluded. 1:1 propensity score matching was performed using variables available up to and including the date of menopause diagnosis, including demographics (e.g., age at index, sex, race, ethnicity), comorbidities (e.g., BMI, hypertension, diabetes, chronic kidney disease, tobacco and alcohol use), nutritional deficiencies and metabolic conditions affecting bone health (e.g., vitamin D deficiency, calcium deficiency, hyperparathyroidism, etc.), and use of other bone-modifying agents such as bisphosphonates, antiresorptive, and anabolic therapies. Primary outcomes were new-onset osteoporosis and stress fractures within 5 years following initial diagnosis.

RESULTS:

Before matching, the non-HRT group included 972,778 individuals and the HRT group 72,670. After matching, 68,742 patients remained in each group with balanced baseline characteristics. By five years of follow-up, the non-HRT group demonstrated a significantly higher risk of developing osteoporosis compared to the HRT group (OR 1.18, 95% CI 1.092–1.284, p < 0.0001). However, there was no significant difference in the incidence of new-onset fractures between the two groups (OR 1.01, 95% CI 0.954–1.07, p = 0.7263).

DISCUSSION AND CONCLUSION:

In this large, propensity-matched cohort of postmenopausal women, early initiation of HRT was associated with a significantly lower risk of developing osteoporosis over a five-year period. No significant difference was observed in fracture risk between the HRT and non-HRT groups. This study is the largest to date to directly compare long-term bone health outcomes in HRT users versus non-users while accounting for a broad range of clinical confounders. These findings add to the growing body of real-world evidence on the skeletal effects of HRT and suggest that early initiation may contribute to improved bone density outcomes during the postmenopausal period.

Risk (n=68742)

Complication	non-HRT	HRT	Risk Ratio	95% CI	p-value
Osteoporosis	1254.0 (1.82%)	1059.0 (1.54%)	1.18	(1.09, 1.28)	<0.001*
Stress Fracture	2243.0 (3.26%)	2220.0 (3.23%)	1.01	(0.95, 1.07)	0.726

Characteristic Name	Before Propensity Score Matching non-HRT (n=972778)	HRT (n=72670)	SMD	After Propensity Score Matching non-HRT (n=68742)	HRT (n=68742)	SMD
Age at Index	51.55 ± 6.03	50.86 ± 6.46	0.11	50.87 ± 6.46	50.86 ± 6.46	<0.01
American Indian or Alaska Native	3005 (0.34%)	262 (0.38%)	0.01	254 (0.37%)	262 (0.38%)	<0.01
Asian	47279 (5.27%)	2954 (4.30%)	0.05	2946 (4.29%)	2954 (4.30%)	<0.01
Black or African American	118838 (13.24%)	7170 (10.43%)	0.09	7115 (10.35%)	7170 (10.43%)	<0.01
Female	868711 (96.80%)	66454 (96.67%)	0.01	66406 (96.60%)	66453 (96.67%)	<0.01
Hispanic or Latino	81559 (9.09%)	5048 (7.34%)	0.06	4978 (7.24%)	5048 (7.34%)	<0.01
Male	1149 (0.13%)	51 (0.07%)	0.02	66 (0.10%)	51 (0.07%)	0.01
Native Hawaiian or Other Pacific Islander	6098 (0.68%)	268 (0.39%)	0.04	286 (0.42%)	268 (0.39%)	<0.01
Not Hispanic or Latino	579635 (64.59%)	46962 (68.32%)	0.08	47018 (68.40%)	46961 (68.32%)	<0.01
Other Race	26045 (2.90%)	2089 (3.04%)	0.01	2070 (3.01%)	2089 (3.04%)	<0.01
Unknown Ethnicity	236281 (26.33%)	16733 (24.34%)	0.05	16746 (24.36%)	16733 (24.34%)	<0.01
Unknown Gender	27615 (3.08%)	2238 (3.26%)	0.01	2270 (3.30%)	2238 (3.26%)	<0.01
Unknown Race	106976 (11.92%)	8178 (11.90%)	<0.01	8188 (11.93%)	8178 (11.90%)	<0.01
White	589234 (65.66%)	47822 (69.57%)	0.08	47873 (69.64%)	47821 (69.57%)	<0.01
Alcohol abuse	8749 (0.98%)	657 (0.96%)	<0.01	607 (0.88%)	657 (0.96%)	0.01
Alcohol dependence	5626 (0.63%)	441 (0.64%)	<0.01	396 (0.58%)	441 (0.64%)	0.01
Alcohol use, unspecified	3351 (0.37%)	248 (0.36%)	<0.01	208 (0.30%)	248 (0.36%)	0.01
BMI	30.35 ± 7.72	29.57 ± 7.65	0.1	29.88 ± 7.58	29.57 ± 7.65	0.04
Chronic kidney disease (CKD)	13772 (1.54%)	995 (1.45%)	<0.01	877 (1.28%)	995 (1.45%)	0.01
Complications and ill-defined descriptions of heart disease	16597 (1.85%)	1139 (1.66%)	0.01	1077 (1.57%)	1139 (1.66%)	0.01
Diabetes mellitus due to underlying condition	4265 (0.48%)	310 (0.45%)	<0.01	249 (0.36%)	309 (0.45%)	0.01
Drug or chemical induced diabetes mellitus	2993 (0.33%)	218 (0.32%)	<0.01	191 (0.28%)	217 (0.32%)	0.01
Essential (primary) hypertension	232386 (25.89%)	15180 (22.08%)	0.09	15077 (21.93%)	15180 (22.08%)	<0.01
Malnutrition	3703 (0.41%)	353 (0.51%)	0.01	274 (0.49%)	352 (0.51%)	0.02
Other specified diabetes mellitus	5243 (0.58%)	377 (0.55%)	<0.01	330 (0.48%)	376 (0.55%)	0.01
Overweight and obesity	170833 (19.04%)	12049 (17.53%)	0.04	11881 (17.28%)	12049 (17.53%)	0.01
Tobacco use	23942 (2.67%)	1472 (2.14%)	0.03	1414 (2.06%)	1472 (2.14%)	0.01
Type 1 diabetes mellitus	7690 (0.86%)	553 (0.80%)	0.01	522 (0.76%)	552 (0.80%)	<0.01
Type 2 diabetes mellitus	86168 (9.60%)	5455 (7.94%)	0.06	5335 (7.76%)	5455 (7.94%)	0.01
Dietary calcium deficiency	344 (0.04%)	29 (0.04%)	<0.01	18 (0.03%)	29 (0.04%)	0.01
Disorder of phosphorus metabolism, unspecified	796 (0.09%)	69 (0.10%)	<0.01	45 (0.07%)	69 (0.10%)	0.01
Familial hypophosphatemia	617 (0.07%)	63 (0.09%)	0.01	37 (0.05%)	63 (0.09%)	0.01
Hereditary vitamin D-dependent rickets (type 1) (type 2)	618 (0.07%)	62 (0.09%)	0.01	38 (0.06%)	62 (0.09%)	0.01
Hypercalcemia	6714 (0.75%)	482 (0.70%)	0.01	434 (0.63%)	482 (0.70%)	0.01
Hypocalcemia	4010 (0.45%)	354 (0.52%)	0.01	311 (0.45%)	353 (0.51%)	0.01
Hypomagnesemia	5969 (0.67%)	552 (0.80%)	0.02	449 (0.65%)	552 (0.80%)	0.02
Hypoparathyroidism	994 (0.11%)	73 (0.11%)	<0.01	45 (0.07%)	73 (0.11%)	0.01
Iron deficiency	9032 (1.01%)	853 (1.24%)	0.02	814 (1.18%)	853 (1.24%)	0.01
Other disorders of phosphorus metabolism	2505 (0.28%)	247 (0.36%)	0.01	165 (0.24%)	247 (0.36%)	0.02
Vitamin D deficiency	132619 (14.78%)	9351 (13.60%)	0.03	9270 (13.49%)	9351 (13.60%)	<0.01
abaloparatide	10 (0.00%)	0 (0.00%)	<0.01	0 (0.00%)	0 (0.00%)	
alendronate	936 (0.10%)	73 (0.11%)	<0.01	63 (0.09%)	73 (0.11%)	<0.01
denosumab	274 (0.03%)	15 (0.02%)	0.01	20 (0.03%)	15 (0.02%)	<0.01
ibandronate	177 (0.02%)	19 (0.03%)	0.01	14 (0.02%)	19 (0.03%)	0.01
raloxifene	402 (0.05%)	21 (0.03%)	0.01	14 (0.02%)	21 (0.03%)	0.01
risedronate	171 (0.02%)	17 (0.03%)	<0.01	10 (0.02%)	17 (0.03%)	0.01
romosozumab	10 (0.00%)	10 (0.02%)	0.02	0 (0.00%)	10 (0.02%)	0.02
salmon calcitonin	83 (0.01%)	10 (0.02%)	<0.01	10 (0.02%)	10 (0.02%)	<0.01
teriparatide	14 (0.00%)	10 (0.02%)	0.01	0 (0.00%)	10 (0.02%)	0.02
zoledronic acid	463 (0.05%)	28 (0.04%)	0.01	30 (0.04%)	28 (0.04%)	<0.01