

Investigation of Bone-Mineral Density while using Thyroid Medication: a SWAN Cohort Study

by

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Abstract

Hypothyroidism, a condition of decreased thyroid hormone secretion, can result in severe skeletal deficiencies. These deficiencies can result in impaired bone maturation and have been associated with an increased risk for bone fractures. Although numerous studies have examined the effect of thyroid hormones on the change in bone mineral density (BMD), they are inconsistent in their results. None have constrained for new users to thoroughly investigate the effect of the medication on the bone. This is problematic because including both incident and prevalent users in the analysis may lead bias. Our objective is to estimate the effect of thyroid medication use on BMD in women with hypothyroidism during the menopausal transition.

We investigated the annual percent BMD loss in the lumbar spine, femoral neck, and total hip among women who initiated thyroid medication for hypothyroidism in the Study of Women's Health Across the Nation (SWAN). We used the "new user" design, which classifies persons as "users" if they are incident users rather than prevalent users. Propensity score (PS) matching was used to obtain a comparable group of women who initiated medication and women who did not initiate medication. Mixed-effects regression modeling was used to compare the longitudinal annualized rate of change in BMD at a given site using covariates that have a potential effect on bone health.

Both thyroid hormone users (N=209) and non users (N=209) lost BMD at each of the measured sites over time. The difference in the mean annualized percent for the change in BMD between the thyroid medication user group and the non-user group was not statistically

significant at the lumbar spine (-0.208 vs -0.139; $p = 0.561$), the femoral neck (-0.582 vs -0.415; $p = 0.183$), nor the total hip (-0.455 vs -0.372; $p = 0.455$). These results suggest that thyroid hormone use does not have a significant effect on BMD .

Public Health Significance: Hypothyroidism is expected to increase as the population ages. Determining if and how initiating thyroid treatment for hypothyroidism is associated with relevant health outcomes could prove to be significant for public health practice.

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1.0 Introduction

1.1 The Thyroid: An Overview

1.1.1 Role of the Thyroid Gland and Thyroid Hormones

The thyroid gland, regulated by the hypothalamus and the pituitary gland, is essential to the functioning of the endocrine system (1, 2). Along with the nervous system and immune system, the thyroid gland regulates most important metabolic pathways (2, 3). Normal functioning of the thyroid gland is maintained by a negative feedback loop involving the hypothalamic-pituitary-thyroid axis (4, 5). Thyrotropin releasing hormone (TRH), produced in the hypothalamus, incites the production and secretion of thyroid stimulating hormone (TSH) in the pituitary gland (1, 2). TSH stimulates the thyroid gland in the synthesis of two hormones, the bioactive triiodothyronine (T3) and the prohormone thyroxine (T4). T4 and T3 are synthesized and secreted by the thyroid gland in an approximated 10:1 ratio. T4 is converted into T3 through deiodination (removal of an iodine atom) in peripheral tissues, most commonly in the liver (6, 7). Thyroid hormones regulate metabolic pathways, growth, and bone development (3). Specifically, TSH has been explicitly proposed as an inhibitor of bone turnover (4). Bone turnover regulates and maintains our calcium homeostasis to repair microfractures and defective bone (8). Under normal conditions for the hypothalamic-pituitary-thyroid axis, the negative feedback loop is maintained by TRH promoting production of TSH, which in turn stimulates the production of T3 and T4, who inhibit the production of both TRH and TSH. When normal functioning of this axis

is disrupted resulting in high T3 and T4 or low T3 and T4, two conditions can develop, thyrotoxicosis, or hyperthyroidism, and hypothyroidism.

1.1.2 Thyroid Disorders

1.1.2.1 Pathophysiology of Thyrotoxicosis (Hyperthyroidism)

As the thyroid gland secretes more T3 and T4 hormones than the body needs, thyrotoxicosis (also called hyperthyroidism) can develop (5). Thyrotoxicosis and hyperthyroidism will be used interchangeably for the purposes of this paper. Due to the negative feedback loop of the hypothalamic-pituitary-thyroid axis, elevated levels of T3 and T4 hormones indicate the suppression of TSH levels (5). With TSH suppressed, bone turnover remains uninhibited, which results in bone loss (5).

1.1.2.2 Pathophysiology of Hypothyroidism

Hypothyroidism results from a deficiency in thyroid hormones T3 and T4 (7). While hypothyroidism is frequently a primary process whereby the thyroid gland is unable to produce sufficient amounts of T3 and T4, it can also develop from a secondary and tertiary process. In the secondary process, the thyroid gland receives insufficient stimulation from a lack of TSH secreted by the pituitary gland. While in the tertiary process, TRH is insufficiently released from the hypothalamus, resulting in an insufficient release of TSH and thus thyroid hormones (7).

Under primary hypothyroidism, the negative feedback loop of the hypothalamic-pituitary-thyroid axis results in increasing TSH levels that could result in a suppression of bone turnover. The ability to repair defective bone and microfractures may therefore be limited for individuals. Under the secondary and tertiary processes, insufficient TSH can result in a higher rate of bone turnover as in thyrotoxicosis (hyperthyroidism), resulting in bone loss. That is, under different conditions, both hyperthyroidism and hypothyroidism could lead to higher rates of bone turnover. Bone turnover and bone formulation need to be balanced for proper bone strength.

The thyroid regulates the metabolism; thus, hypothyroidism triggers important metabolic changes. These changes include hyperlipidemia, coagulopathy, endothelial dysfunction, hypertension, and other cardiovascular disorders (9). There have been conflicting results regarding the role of hypothyroidism in fracture risk. A nationwide study in Denmark found an increased fracture risk in people with hypothyroidism, before and after diagnosis, when compared with age- and gender- matched controls (10). Another study of subclinical hypothyroidism in American men and women aged 65 and older found no association between hypothyroidism and BMD at the lumbar spine, total hip, or femoral neck sites (11). Other studies have suggested that hypothyroidism is unlikely to increase the risk of fractures per se, but that long-term replacement of thyroid hormones due to the hypothyroidism may result in an increased risk for fractures (6). Long-term effects of hypothyroidism on the body remains a topic of discussion.

1.1.2.2.1 Epidemiology of Hypothyroidism

In the United States, 4.6 percent of people aged 12 and older have some type of hypothyroidism, so that it affects almost five people out of 100 (12). Like thyrotoxicosis, women are more likely to develop hypothyroidism than men, and those aged 60 and older are at an increased risk for the development of hypothyroidism. This risk is more pronounced for those aged 80 and older, for example, NHANES 1999-2002 found five-time greater odds of developing hypothyroidism among those 80 and older compared to individuals aged 12-49 (13).

1.1.2.2.2 Pharmacotherapy of Hypothyroidism & Other Outcomes

Levothyroxine is a synthetic levoisomer of T4 and is the most common drug prescribed to treat hypothyroidism. Liothyronine—a manufactured form of T3—and Liotrix—a mix of T3 and T4—are other drugs within the therapeutic arsenal to treat hypothyroidism (14, 15). Levothyroxine works by acting as the supplemental, synthetic thyroid hormone that is usually produced by the thyroid gland, T4 (12, 16). The synthetic T4 hormone, like in the natural process, creates T3 through deiodination. Treatment can reverse the signs and symptoms associated with hypothyroidism, including include poor growth, lack of energy, joint and muscle pain (2, 17, 18). Those who receive adequate treatment for hypothyroidism can expect a normal life expectancy (17). However, if treatment is not adequate, hypothyroidism can progress, resulting in a life-threatening myxedema coma or death (17). Side effects of treatment for hypothyroidism can include changes in menstrual cycle, joint pain, and leg cramps.

Moreover, when looking at quality of life measured using health-related quality of life (HRQL) questionnaires, patients with untreated thyroid disease suffered from a comprehensive list of symptoms and had major impairment in most areas of HRQL (19). This reduced quality of life persists long-term, even when normal thyroid functioning has returned (9).

1.2 Bone Mineral Density (BMD)

1.2.1 Epidemiology of BMD

Low bone mass is a mild form of osteoporosis, defined as having a bone mineral density (BMD) value between 1.0 and 2.5 standard deviations below the documented mean value for a young non-Hispanic white female reference group (20). Osteoporosis is defined as having a BMD value that is more than 2.5 standard deviations below the mean value for a young non-Hispanic white female reference group (20). An estimated 10.2 million adults over age 50 had osteoporosis at the femoral neck or lumbar spine in a 2010 estimate, while 43.4 million adults had low bone mass at these sites (21). The prevalence of low BMD increases with age, with the prevalence of osteoporosis in men being three times higher for those over 80 than compared to 50-79 (21). Women are more likely than men to develop both osteoporosis, 24.8% compared to 5.6%, and low bone mass, 52.3% and 44.0%, at either skeletal site (20). The prevalence of low BMD is expected to continue to rise due to America's increasingly aging population (22).

1.2.2 Effects of Bone Mineral Density on Health Outcomes

As bone mineral density decreases to osteoporotic levels, fracture, the need for long-term care, and excess mortality can become clinical and health-related concerns (22). Once osteoporotic fractures occur, they have been shown to be associated with increased risk for morbidity and mortality in some studies, but this association has not been observed in other studies (22). Hip fractures in particular result in a 10 percent to 20 percent increase in mortality risk within one year (22). Once a fracture occurs, the risk of future fractures increases 2.5 times after a fracture occurs, and the odds of disability rise to 3.33 in older women (>65 years old) (22, 23). Moreover, hip fractures increase the risk of mortality by 10 to 20 percent, and approximately 20 percent of individuals who suffer hip fractures need long-term care (22). The majority of these individuals will never regain their previous level of mobility (22). An association between BMD and fractures was not observed by Garin et al., whose study of subclinical hypothyroidism in 4,936 American men and women over age 65 found no relationship between BMD and new hip fractures (11).

Though quality-of-life estimators vary according to the site of the fracture, comorbidity, mobility, activities of daily life (ADL)-independence, and fracture complaints, it is accepted that fractures, particularly hip fractures, result in a diminished quality of life (24). Since quality of life is not fully restored after a hip fracture, prevention of fractures is an important way to maintain quality of life (24). These effects of BMD on fracture risk and other health outcomes emphasize the public health importance of researching how BMD is affected. In 2005, Americans spent between 13.7 billion dollars and 20.3 billion dollars on direct medical costs for

Osteoporosis (22). This total cost is expected to rise to 20.5 billion dollars in 2025 as the US population ages, further underscoring the public health significance of this issue (22).

1.2.3 The Menopausal Transition and Bone Mineral Density

The menopausal transition is a major health milestone that has implications for women beyond reproduction. Bone mineral density loss starts during the menopausal transition, prior to the final menstrual period, and extends beyond the final menstrual period (25). This phenomenon was corroborated through SWAN, finding that the greatest bone loss occurred one year prior to the final menstrual period and decelerated, but did not cease, through two years after the final menstrual period (26). At both the lumbar spine and the femoral neck, this loss is seen greatest from one year prior to the final menstrual period through two years after the final menstrual period (26). The greatest decline in BMD occurs during late perimenopause, while little decline is seen during early perimenopause (Figure 1, 2) (26). Postmenopausal loss rates are less than those seen during perimenopause (26). The loss in BMD over the menopausal transition is influenced by both race/ethnicity and BMI, where African American heritage and higher BMI were associated with slower BMD loss (26, 27). The opposite association is seen for those of Japanese and Chinese and lower BMI (26). It has been proposed that this association between bone strength during the menopausal transition and race/ethnicity is actually due to confounding by BMI and age (28).

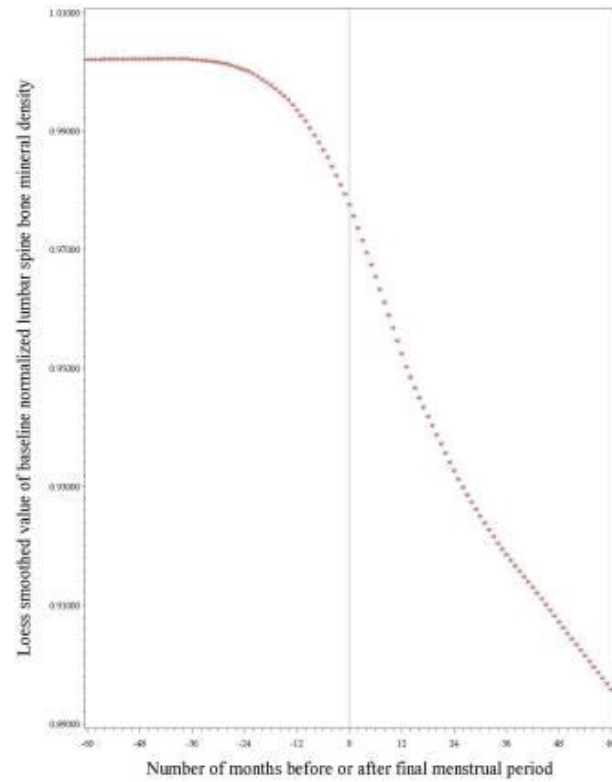


Figure 1. BMD Loss Over the Menopausal Transition at the Lumbar Spine (26)

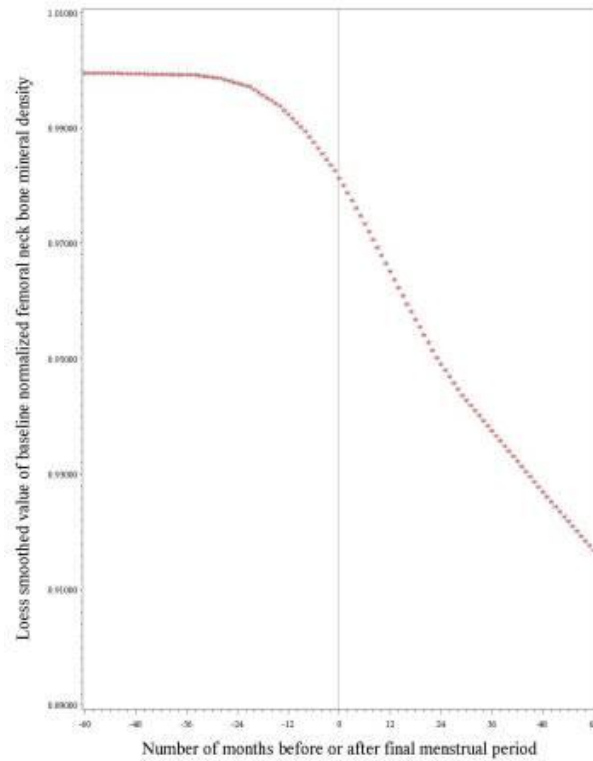


Figure 2. BMD Loss Over the Menopausal Transition at the Femoral Neck (26)

1.3 The Thyroid and Bone Mineral Density

1.3.1 Thyroid Hormones and BMD

While a low level of thyroid hormone secreted by the thyroid gland directly leads to hypothyroidism, studies are inconsistent about the effect of thyroid hormones on BMD. A study measuring BMD by dual x-ray absorptiometry, bone geometry by peripheral quantitative computed tomography (pQCT), and bone strength by finite element analysis showed no significant difference between the 49 patients who received T4 for hypothyroidism and controls (29). Yet another study including 26 premenopausal women who were prevalent users of T4 found a reduced BMD in these women compared to controls (6). Low sample size and variability in patient adherence to hormone therapy and thus sustainment of restored thyroid functioning hinder the generalizability and interpretability of studies to date (6).

1.3.2 Thyroid Treatment and Bone Mineral Density

Long-term trends in the relationship between Levothyroxine (T4) therapy and BMD are controversial. In premenopausal women taking Levothyroxine for at least five years, a 12.8 percent lower BMD at the femoral neck and a 10.1 percent lower BMD at the femoral trochanter was observed compared to women without thyroid or bone abnormalities (30). A higher prevalence of low BMD was again seen in a group of women taking Levothyroxine after a thyroidectomy compared to women without thyroid diseases (31). This relationship was not observed in a different group of women who had undergone thyroidectomy, where no difference

in BMD was detected at any of the bone sites as compared to women with no thyroid abnormalities (32). These 3 studies were relatively small with 31, 49, and 50 study participants, respectively, highlighting the need for a larger, more robust investigation to clarify the relationship between treatment and BMD among women with an under-functioning thyroid.

1.4 SWAN

The Study of Women's Health Across the Nation (SWAN) is a multisite, longitudinal study examining the health of women across and during the menopausal transition. Starting in 1996, 3,302 women aged 42 to 52 were enrolled and followed over a maximum of 16 annual follow-up visits after baseline. At each visit, women were interviewed and asked to answer a variety of questions, including questions regarding “menstrual bleeding patterns, clinical health history, health behaviors, and psychosocial factors; sexual health, assessment of anthropometric measures, physical performance, and cognitive function; and provision of blood and urine samples” (27). Some sites have also collected data for body composition and BMD; radiographic knee osteoarthritis; subclinical cardiovascular atherosclerosis; and sleep measures (27).

SWAN data is uniquely positioned to address the gaps in knowledge related to treatment for hypothyroidism and changes in BMD over the menopausal transition due to its longitudinal nature over the menopausal transition, collection of a wide variety of lifestyle behaviors, symptoms, and healthcare utilization annually for up to 16 years after baseline, and large group of multiracial/ethnic women across seven distinct sites in the United States (27). Emphasis was placed on enrolling a community-based population rather than volunteer or clinic based, so the

sample of women in this study is more generalizable to an American population and the results can be interpreted in this context (25).

1.5 Gaps in Knowledge

Several important gaps remain to be researched regarding the effect of treatment with thyroid hormones on BMD among women with hypothyroidism. Though several studies have analyzed the effect of thyroid hormone use on BMD, most have had small sample sizes and limited or no follow-up time. Moreover, prior studies have not followed patients from the initiation of thyroid hormones, which is concerning because selection bias can occur if prevalent users are included in the analysis since they are “survivors” of the early period of treatment; the effects of treatment may be different short term compared to long term since the cumulative effects of the medications may impact outcomes. Furthermore, once using treatment, those who continue treatment are often different than those who discontinue treatment since the decision to discontinue treatment is frequently determined from the early response to treatment. Using incident users of treatment in analysis avoids these concerns. Additionally, some studies have attempted to distinguish the effect on the bone of the disease hypothyroidism as compared to the thyroid hormones in an attempt to handle confounding by indication. A clear, robust delineation of these effects is challenging and remains to be resolved.

1.6 Public Health Significance

Hypothyroidism is a common condition in America and its prevalence is expected to increase as the population ages. Defining the effect of thyroid medication use on BMD in women with hypothyroidism will orient the development of clinical guidelines, ultimately preventing fractures and saving related costs. Women with hypothyroidism going through the menopausal transition may be particularly vulnerable to negative health outcomes due to the potential dual effects of hypothyroidism and menopause on accelerated bone loss. Determining whether the initiation of thyroid treatment for hypothyroidism traversing the menopausal transition is associated with relevant health outcomes could prove to be significant for public health practice.

2.0 Objective

2.1 Aim 1: Evaluate and define the effect of thyroid medication use on BMD in women with hypothyroidism.

The objective of this research is to estimate the association between thyroid medication use and BMD at three different sites, including the lumbar spine, the femoral neck, and total hip, among women who initiate medication use for hypothyroidism compared to analogous controls who have not been clinically diagnosed with hypothyroidism and are not using thyroid medication. We aim to utilize established pharmaco-epidemiology methods to minimize the bias of these estimates. Our hypothesis is women who use thyroid hormones for hypothyroidism will have a greater decline in BMD than their analogous controls over the menopausal transition adjusting for demographic characteristics, clinical history, medication use, and substance use.

3.0 Methods

3.1 Study Population

SWAN data was collected from 3,302 women across seven locations in the United States: Boston, Chicago, the Detroit area, Los Angeles, Newark, Pittsburgh, and Oakland (25, 26, 33). Each field site was required to collect data from non-Hispanic Caucasian women and one minority group, which include African Americans, Chinese, Hispanic, and Japanese (25, 26, 33). The number of individuals recruited for each minority population was specific to each site. The number of minority individuals recruited was based on the specific minority population being evaluated, the characteristics of the site, and the optimal ability for answering the Study's scientific questions (25). To be eligible for enrollment in SWAN, women needed to be aged 42-52 years, not had their uterus and/or both ovaries surgically removed, not currently using exogenous hormone preparations affecting ovarian function, have had at least one menstrual period in the previous three months, and self-identified as a racial/ethnic population of interest for the respective field site (25, 26, 33). To recruit study participants, each site used a random digit dialing-based sampling frame or a list-based sampling frame (25).

3.2 Bone Substudy and Outcome Measure

Bone mineral density was measured at baseline and 15 follow-up visits over the course of two decades at the lumbar spine, proximal femur, and total hip (g/cm^2) at five field sites in SWAN: Pittsburgh, Oakland, Boston, Detroit area, and Los Angeles (34). 2,335 participants were enrolled in the bone cohort. Participants who were prevalent hormone therapy users were excluded (26).

Our outcome measure was defined as the mean annualized change in BMD. The raw BMD measurements were converted to baseline-normalized percent BMD values for interpretability. For each individual, BMD was defined as 100% at the individual's baseline visit, and the change in BMD is defined as 100 times the ratio of the follow-up BMD measurement at each follow up visit divided by the baseline BMD measurement (35). For the purposes of our paper, "baseline" is defined for thyroid medication users as the index visit upon which they initiated use of thyroid medication; "baseline" for analogous non users is defined as the index visit upon which their matched user initiated medication. For each participant, annualized BMD was analyzed up to three visits before baseline and up to 14 visits after baseline.

Measurements of BMD were made with the Hologic 2000 and 4500A densitometers (26, 36). Each site calibrated their devices daily using an anthropomorphic spine phantom, every six months with a spine phantom circulated to all sites, and routinely audited five percent of all scans and scans with potential problems using Synarc, Inc (Waltham, MA) (36, 37). BMD measurements by dual-energy X-ray absorptiometry DXA captures areal BMD (g/cm^2), which introduces a bone size scale artifact. To address this artifact, bone mineral apparent density (BMAD) is calculated to measure the geometry of bones using the formula $\text{BMAD} = \text{BMD} /$

square root BA (where BA = bone area) (38). BMAD was calculated for each site to address differences in bone size and thickness (38).

3.3 Exposure of Interest

The exposure of interest is the initiation of medication for hypothyroidism. Medication for hypothyroidism was defined as initiation of one of three medications: Levothyroxine, Liothyronine, or Liotrix. Prevalent users of medication for hypothyroidism at SWAN enrollment were excluded from this analysis. Non users were not required to have clinically diagnosed hypothyroidism but they were selected to be comparable to the users with respect to demographic characteristics, clinical history, medication use, and substance use.

3.4 Covariates

At each annual visit, standardized interviewer-administered or self-administered questionnaires were used to assess: height (m), weight (kg), age (years), smoking status, alcohol intake (drinks per days), vitamin D intake (international units per day), calcium intake (milligrams per day), medication use, and menopausal status (39). Use of bone positive treatments, which includes bisphosphonates, tamoxifen, hormone replacement therapy, gonadotropins, selective estrogen receptor modulators (SERMS), and parathyroid hormone, and bone negative treatments, including oral steroids, gonadotropin-releasing hormone (GnRH), antineoplastics, antiepileptics, and aromatase inhibitors, were also recorded. Body mass index (BMI) was calculated using the measured height and weight. Menopausal status was

characterized as premenopausal if the participant experienced one menstrual period within the last three months with no irregularities in the last year, perimenopausal if the participant experienced menstrual bleeding during the past 11 months but not within the last three months, and postmenopausal if the participant did not experience any menstrual bleeding for 12 consecutive months (39). The final menstrual period was defined as the last menstrual bleeding date reported during the participants' previous visit. Menopausal status was classified as a unidirectional transition.

Other measurements assessed included demographic characteristics, including income, education, and marital status, self-reported health status, social support, which includes items from the 20 item Medical Outcomes Study Social Support Survey, vasomotor symptoms, and self-reported comorbid conditions, such as osteoporosis, thyroid disease, cancer status, and diabetic status. A modified version of the Baecke Physical Activity Questionnaire was also used to evaluate physical activity (34).

3.5 New User Design

The “new user design” is a pharmaco-epidemiology study design used in observational studies to classify persons as medication users if they are incident users rather than prevalent users. Prevalent users are excluded in the new user design. New users are identified at the initiation of treatment. The visit when each participant initiates treatment then becomes her “index start date”. Non user controls are matched to users based on pre-specified criteria, and their “index start date” is the same visit as their matched user's. The main advantage of the new user design is the reduction of bias. It reduces selection bias since prevalent users are excluded;

prevalent users are “survivors” of the early period of treatment (40). Covariates for drug users also may be affected by the drug itself, which makes them difficult to adjust for without introducing possible confounding into the study (40). The new user design eliminates these biases by starting observation at the initiation of the treatment (40).

3.6 Data Analysis

The visit at which a woman initiated medication for the thyroid hormone users was identified and labeled as the baseline visit for this analysis. For women not initiating medications, frequency matching was used to obtain a similar distribution of baseline visits. Propensity score matching was used in a 1:1 ratio to obtain a comparable control group of non-users. The outcome for our propensity score was binary medication use (yes/no), and the final propensity score model included the covariates: age, BMI, femoral neck BMD, lumbar spine, total hip BMD, tobacco use, alcohol use, race/ethnicity, menopausal status, medication use, including bone positive medications, bone negative medications, thiazide, and comorbid conditions, including osteoarthritis, osteoporosis, cancer, and diabetes. The greedy matched algorithm was used to match the logit of the propensity score using a maximum caliper of width equal to 0.2 of the standard deviation of the logit of the propensity score. Descriptive statistics of baseline demographic variables were calculated for this cohort. Standardized differences (SMD) in covariate means were calculated to assess the balance and comparability between the selected user and non-user groups. An acceptable SMD value ranged from 0-0.2. The propensity score matching was adjusted to include additional covariates or interactions, as needed, in order to improve balance.

Once the matched thyroid hormone user and non-user groups were finalized, mixed-effects regression modeling was used to compare the longitudinal annualized rate of change in BMD at a given site (i.e. lumbar spine, femoral neck and total hip) between the users and non-users. The outcome variable for the lumbar spine, femoral neck, and total hip BMD models were the longitudinal BMD values for the current visit divided by baseline BMD value. A random intercept and slope for each woman was used to control for within-person correlation. We entered medication use, age, race, site, BMI, and menopausal status, a priori, as covariates in the linear mixed model. We then entered the following variables based on their known association with BMD: diabetes, bone positive medications, bone negative medications, diuretics thiazide, alcohol use, smoke status, calcium intake, prevalence of osteoporosis, prevalence of arthritis. Only those variables with p-value <0.05 were retained in the final models. For consistency, the linear mixed models for annualized change in BMD at each site were created to include the same covariates.

Time after baseline (in years) and the interaction between time and medication use were included in the models. After multiplying the coefficients by 100, the coefficient of the “time” variable can be interpreted as the estimated percent change per year in BMD for the non user group, and the interaction term between medication use and time as the difference in annualized percent change in BMD for the user group compared to the non-user group. Therefore, to obtain the annualized percent change in BMD for the user group, we added the coefficient of “time” with the coefficient for the interaction. SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina) was used for the analysis.

4.0 Results

4.1 Patient Characteristics

Figure 3 shows the selection of the study sample for this analysis. Of the N=2,365 women registered in the SWAN bone cohort, 141 participants were excluded due to being prevalent users of thyroid hormones at baseline. Of the remaining N=2,224 participants, N=225 were incident thyroid hormone users at baseline and N=1,999 participants - classified as non users of thyroid hormones. Using a random frequency matching process, of the N=225 hormone users, six participants were excluded due to having thyroid cancer at baseline, and another six participants were excluded due to not having any previous visits in SWAN prior to the baseline bone cohort measurements, leaving N=213 incident hormone users. Of the N=1,999 non users of hormones, two were excluded due to having thyroid cancer at baseline, and another 284 participants were excluded due to not being matched at baseline (absent or lacked follow-up visit for matched baseline visit), leaving N=1,713 non users of hormones.

The propensity score model that was used to derive the predicted probability of medication use for hypothyroidism for each woman is shown in Table 1. No additional covariates or interactions were added to the model. Applying the propensity score matching algorithm, N=209 users and N=209 matched non users were identified in the dataset (Figure 3).

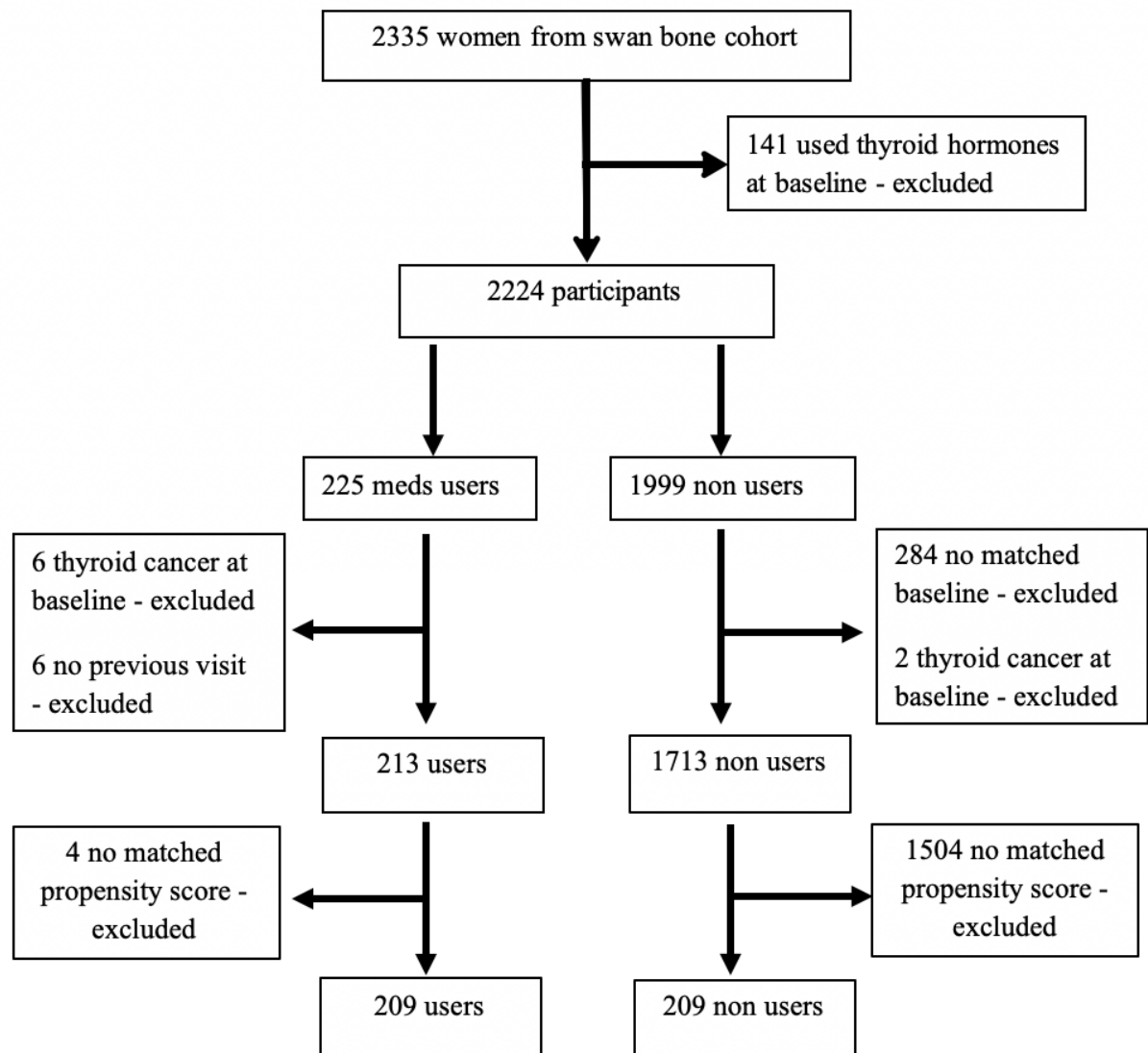


Figure 3. Flowchart of Study Cohort

Table 1. Derived Propensity Score Model

Logistic Regression Modeling Y = Use of therapy for hypothyroidism yes/no				
Parameter	Estimate	OR Point Estimate	95% Wald Confidence Limits	
Intercept	-3.7866			
Age	0.00196	1.002	0.985	1.020
BMI	-0.00663	0.993	0.970	1.017
Education Level	-0.1963	0.822	0.584	1.155
Race	0.4984	1.646	1.364	1.987
Smoking Status	-0.2283	0.796	0.644	0.984
Alcohol Category	0.0525	1.054	0.902	1.231
Early/Late Perimenopausal (Ref Postmenopausal)	0.4705	1.601	1.096	2.337
Premenopausal (Ref Postmenopausal)	-0.1390	0.870	0.411	1.844
Unknown Menopausal Status (Ref Postmenopausal)	-0.3906	0.677	0.401	1.141
Dummy Variable (Ref Postmenopausal)	2.5654	13.006	1.402	162.366
Diabetes	-0.2607	0.711	0.457	1.298
Imputed Osteoporosis	1.2842	3.612	0.597	21.850
Imputed Osteoarthritis	0.2550	1.290	0.140	11.904
Cancer Status at Current Visit	0.3237	1.382	0.938	2.037
Any Bone Positive Medications	0.6457	1.907	1.206	3.016
Any Bone Negative Medications	0.1878	1.207	0.731	1.993
Diuretics Thiazide	0.3028	1.354	1.094	1.675
Overall Health	0.4193	1.521	1.284	1.801

At the date of medication initiation, the mean age of participants included in this analysis was 51.90 ± 9.47 years old, and the mean BMD was 29.06 ± 7.13 (Table 2). Overall, the femoral neck BMD, lumbar spine BMD, and total hip measured at baseline was 0.81 ± 0.13 , 1.04 ± 0.15 , and 0.94 ± 0.14 g/cm², respectively. The majority of participants had greater than a high school education (77.75%). About 41.45% of participants were either current or past tobacco users, and 48.56% of participants did not drink alcohol at all. Participants were nearly evenly distributed across the five sites, with the lowest number of participants being from the Los Angeles area (17.46%, n = 73) and the highest number of participants being from the Detroit area (22.49%, n = 94). Many of the participants were white (64.59%). Most participants were either perimenopausal (36.12%) or postmenopausal (47.62%) at the time of treatment initiation. While some participants used bone positive medications (21.53%), other participants used bone negative medications (11.24%), and yet another 17.7% were users of Thiazide at baseline. Amongst those with comorbid conditions, 0.24% (n=1) had osteoarthritis, 1.20% (n=5) had osteoporosis, 3.55% (n=1) had cancer, and 10.77% (n=45) had diabetes. All standardized mean differences between the matched user and the non-user groups were below 0.2.

Table 2. Demographic Characteristics of Participants Overall and Stratified by Group

Baseline Characteristics of Propensity Matched Non-Users and Users				
Characteristic	Total	Non-Thyroid Med User	Thyroid Med User	SMD
Med Initiation	n = 418	n = 209	n = 209	
	n (%) or mean $\pm$ SD	n (%) or mean $\pm$ SD	n (%) or mean $\pm$ SD	
Age (years)	51.90 ($\pm$ 9.47)	52.00 ($\pm$ 9.39)	52.00 ($\pm$ 9.57)	0.01
BMI	29.06 ($\pm$ 7.13)	29.08 ($\pm$ 7.34)	29.05 ($\pm$ 6.92)	0.04
Femoral Neck BMD (g/cm ²)	0.81 ($\pm$ 0.13)	0.81 ($\pm$ 0.14)	0.81 ($\pm$ 0.12)	0.04
Lumbar Spine BMD (g/cm ²)	1.04 ($\pm$ 0.15)	1.04 ($\pm$ 0.17)	1.04 ($\pm$ 0.14)	0.02
Total Hip BMD (g/cm ²)	0.94 ($\pm$ 0.14)	0.95 ($\pm$ 0.15)	0.94 ($\pm$ 0.14)	0.03
Educational Attainment				
$\leq$ high school	90 (21.53)	43 (20.57)	47 (22.49)	0.08
GT high school	325 (77.75)	165 (78.95)	160 (76.56)	
Tobacco Use				
current (or past)	172 (41.45)	91 (43.75)	81 (39.13)	0.05
Alcohol Use				
None	203 (48.56)	98 (46.89)	105 (50.24)	0.14
<1/wk	89 (21.29)	46 (22.01)	43 (20.57)	
1-7/wk	66 (15.79)	37 (17.70)	29 (13.88)	
>7/wk	43 (10.29)	20 (9.57)	23 (11.00)	
Site				
Michigan	94 (22.49)	45 (21.53)	49 (23.44)	0.07
Mass General	76 (18.18)	40 (19.14)	36 (17.22)	
UC Davis	84 (20.10)	43 (20.57)	41 (19.62)	
UCLA	73 (17.46)	38 (18.18)	35 (16.75)	
Pittsburgh	91 (21.77)	43 (20.57)	48 (22.97)	
Race/Ethnicity				
White	270 (64.59)	135 (64.59)	135 (64.59)	0.07
Black	89 (21.29)	50 (23.92)	39 (18.66)	
Chinese	39 (9.33)	15 (7.18)	24 (11.48)	
Japanese	20 (4.78)	9 (4.31)	11 (5.26)	
Menopausal Status				
Pre	17 (4.07)	8 (3.83)	9 (4.31)	0.01
Early/Late Peri	151 (36.12)	77 (36.84)	74 (35.41)	
Post (Natural)	199 (47.62)	101 (48.33)	98 (46.89)	
Unknown	50 (11.96)	22 (10.53)	28 (13.40)	
Medication Use				
Bone positive meds	90 (21.53)	45 (21.53)	45 (21.53)	0.12
Bone negative meds	47 (11.24)	24 (11.48)	23 (11.00)	0.03
Thiazide	74 (17.70)	40 (19.14)	34 (16.27)	0.10
Comorbid Conditions				
Osteoarthritis	1 (0.24)	1 (0.48)	0 (0.00)	0.14
Osteoporosis	5 (1.20)	4 (1.91)	1 (0.48)	0.06
Cancer	15 (3.55)	8 (3.79)	7 (3.32)	0.05
Diabetes	45 (10.77)	23 (11.00)	22 (10.53)	0.03

4.2 Changes in Bone Mineral Density

The final linear mixed models for annualized change in BMD included the covariates: age, race, site, BMI, menopausal status, diabetes, bone positive medications, bone negative medications, diuretics thiazide, alcohol use, smoke status, calcium intake, prevalence of osteoporosis, prevalence of arthritis along with the key variables medication use (users vs non-users), time in years, and the interaction between medication use and time. The model was based on 3,291 BMD measurements with 8 median visits ranging from 1 to 14 per woman. On average, both thyroid hormone users and non users lost BMD at each of the measured sites over time (Figure 4). There was not a significant difference in the mean annualized percent for the change in BMD between the thyroid medication user group and the non-user group at the lumbar spine (-0.208 vs -0.139; $p = 0.561$). For BMD measurements of the femoral neck, there was no significant difference in the mean annualized percent change in BMD between thyroid medication users and non-users (-0.582 vs -0.415; $p = 0.183$). There was also no significant difference in BMD measured at the hip (-0.455 vs -0.372; $p = 0.455$).

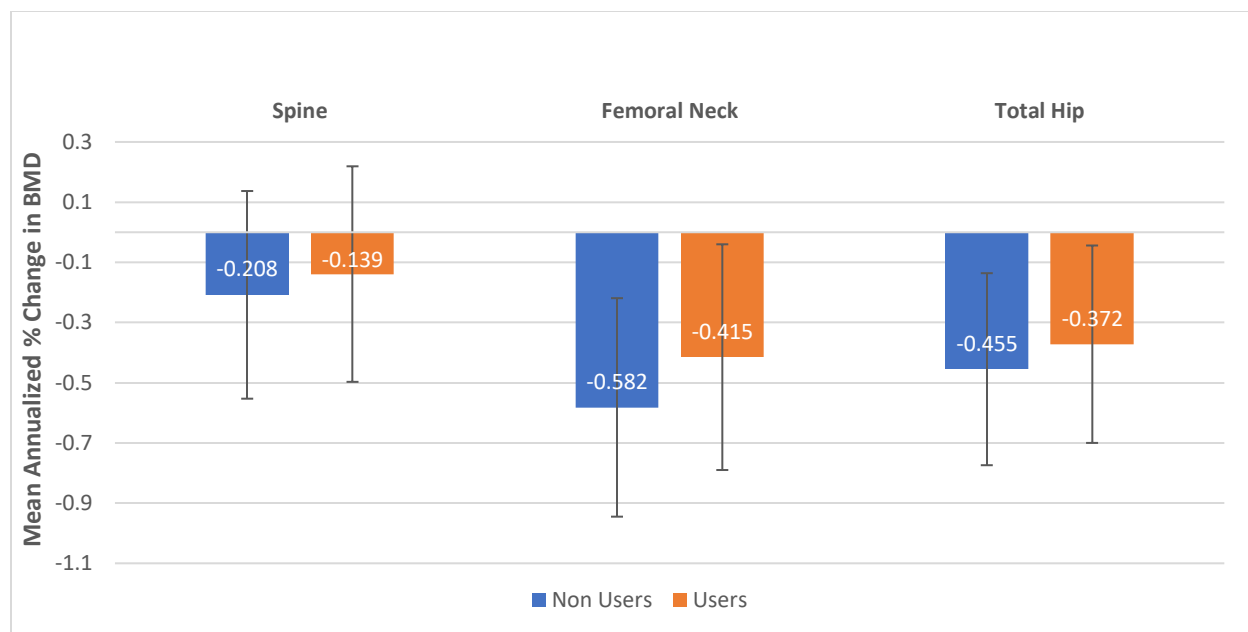


Figure 4. Mean Annualized % Change in BMD

5.0 Discussion

With the objective to estimate the association between the change in BMD and thyroid medication use, our hypothesis was that women who used thyroid hormones for hypothyroidism will have a greater decline in BMD compared to analogous controls who have not been clinically diagnosed with hypothyroidism and who do not use thyroid medication. These racially and ethnically diverse women were sampled from the SWAN cohort, which recruited women at five sites across America, including Pittsburgh, Oakland, Boston, Detroit area, and Los Angeles. Using rigorous methods, we found no significant difference in mean annualized percent change in BMD between users and non users at each of the measured sites, the lumbar spine, femoral neck, and total hip. Hence, our results did not support our hypothesis.

One explanation for this non-significant finding is the detection and treatment of hypothyroidism in this population. With treatment, the signs and symptoms of hypothyroidism can be reversed in most patients (7). Thus, women who receive treatment for hypothyroidism may be expected to have improved bone loss compared to what would be expected if they were not treated.

Previous epidemiological studies on the association between the change in BMD and thyroid medication use have shown mixed results. Franklyn et al. found no association between long-term thyroxine (T4) treatment and BMD when comparing premenopausal women, postmenopausal women, and men of ages 41, 63, and 57 on average, respectively, who had received treatment for up to 19 years (32). These men and women were matched to healthy controls without a history of thyroid disease and that did not use thyroxine (32). Bin-Hong et al. concluded that there was a higher prevalence of low BMD when assessing long-term

levothyroxine treatment in premenopausal women aged 32-45 who received levothyroxine treatment for up to nine years compared to premenopausal women aged 29-45 without a history of thyroid disease and that do not use levothyroxine (31, 32). Treatment for individuals in both studies was a result of a total or near total thyroidectomy (removal of thyroid gland), unlike our study population where treatment was the result of a diagnosis of hypothyroidism. Contrary to these studies who used low sample sizes of 98 and 115 respectively, our study used a larger sample size (418) allowing us to increase power. However, it is possible that our sample size is still too small, thus we lacked the power to detect a difference between the users and non users. Our study was limited by the number of women experiencing the exposure of interest. Power in our analysis could have been improved by increasing the ratio of non users to users during the propensity matching process. Moving forward, we can increase this ratio between non users and users to evaluate if a difference exists between the two groups with a larger power. In assessing the outcome, both studies used DXA to obtain measurements of BMD, equivalent to our study. However, while our study used a longitudinal study design, Franklyn et al. and Bin-Hong et al. conducted cross sectional studies, which included prevalent users. Prevalent users may only be alive and healthy enough to participate in these studies due to their early success in treatment, which can bias results. By using a longitudinal study design and constraining sampling for new medication users, our study minimizes this survivor bias. Our study is therefore an important contribution to the literature because of its larger sample size, the use of longitudinal data over the menopausal transition, and the application of a new user design.

Our findings have important implications. While studies have determined that there are differences in the change of BMD during the menopausal transition among Caucasian women, little is known about the change in BMD for non-Caucasian women (39). Data on longitudinal

rates of bone loss across racial/ethnic groups are also sparse. Limited longitudinal data suggests that the change in elderly African American women is more rapid than in elderly Caucasian women(39). This relationship is mirrored in Chinese and Japanese women compared to Caucasian women, however this loss is nullified when controlling for BMI (39). Our study adds to this body of knowledge in understanding the disparity in BMD across racial/ethnic groups.

Current guidelines from the NIH recommend that women aged 65 and older receive a bone density test (41). Some studies have argued for the reduction in the age of recommendation for screening bone densitometry among thin women, though the exact age is not specified (42, 43). Our results add to this discussion by demonstrating annualized BMD does not change in our population, who have a range of BMIs. With this overall relation more concretely defined, a new policy or recommendation for screening bone densitometry can thus more accurately target the population who would be best served through further analysis of the relationship between BMI and BMD. This analysis can be done by stratifying BMI into groups and comparing users to analogous controls to assess the annualized change in BMD.

While some studies have proposed a delineation between the disease hypothyroidism in contrast to the hormones effect on BMD, our study was limited in that it did not create this distinction. Creating this distinction would necessitate information on the amount (in milligrams) of hormones taken by each woman over the study period. Our study was only interested in the initiation of hormone medication by women with the clinical disease hypothyroidism rather than the amount of hormone medication the women initiated. Further research is necessary to examine if and how these effects on BMD differ.

Despite limitations of our analysis, SWAN data provides unique strengths to answer our research question. With over 2,000 women enrolled in the bone cohort and longitudinal data

collected on physical, biological, psychological, and social changes during the menopausal transition, SWAN data was positioned to answer our research question directly and succinctly. Accordingly, SWAN data addresses the challenges of previous studies plagued by low sample sizes and limited follow-up time. Over 16 annual visits, SWAN obtained BMD measurements from study participants via DXA with proven validity, collected medication use over time, and detailed covariates related to demographic characteristics, clinical history, and substance use, which we used to appropriately adjust for differences between our user and non user groups. Using this detailed data, we were able to focus specifically on women with hypothyroidism and control for variables that influence our outcome. Additionally, using longitudinal data, we could follow women over perimenopause, the period of menopause marked by rapid bone loss, rather than only during pre- and post-menopause. This is important in understanding how medication use affects the rate of bone loss during this period for women with hypothyroidism compared to healthy women for a more robust analysis. Furthermore, the use of pharmaco-epidemiological methods like the new-user design and propensity score matching has allowed us to create largely comparable groups between women who initiated medication and women who did not.

In conclusion, the present study more closely defines the relationship between BMD and thyroid medication use for women with hypothyroidism. We found no significant differences in the mean annualized percent change in BMD between medication users and non users. Being that most women traverse through the menopausal transition, understanding the effect of diseases as we age is of utmost public health significance. Yet still, more work can be done to fully understand this crucial link between BMD and thyroid medication use. In research, particularly in public health, it is important to find results that are not statistically significant as results that are statistically significant. Our research is significant for public health in that our results inform

clinicians seeking the best course of treatment for their patients, allow healthcare systems to better plan for future influxes of conditions and diseases as populations age, and progress the field of research on BMD.

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