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# The Role of Multiple Sclerosis as a Risk Factor for the Development of Osteoporosis

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## Background

- Multiple sclerosis (MS) is an autoimmune progressive neurological disease that leads to early disability of young adults. Reduced mobility and frequent falls, secondary to spasticity and ataxia, increase the risk for osteoporosis. In fact, fractures are a major cause of morbidity and mortality in patients suffering from MS.[1,2] Moreover, many patients with MS and low bone mass or previous fractures are not taking supplemental calcium or vitamin D.[3]
- Several studies have examined the incidence of reduced bone mineral density (BMD) amongst people with MS, and the majority providing evidence that BMD is significantly reduced in MS patients. The most significant risk factors appear to arise from the chronic disease process of MS and not from glucocorticoid use.[3-7] However, the temporal relationship between these two conditions has not been previously studied.
- Fortunately, data from the Women's Health Initiative provides a unique opportunity to examine the development of osteoporosis over time and its relationship to MS. The WHI population is ideal to study because patients will be more likely to reflect the longstanding MS that affects mostly women.
- From longitudinal data (baseline and follow-up studies), the association between MS and osteoporosis can be examined over time and refined by considering the contributions of additional pharmacologic and lifestyle variables. Latency and type of treatment for osteoporosis in MS and non-MS populations can provide insight for clinical recommendations regarding an at-risk population.

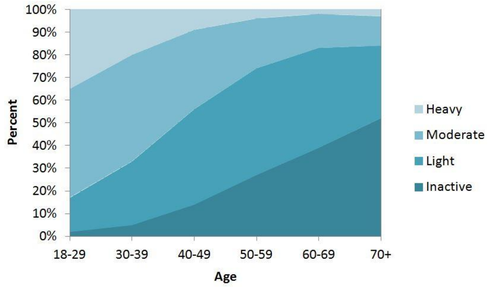


**Figure 1: Activity level according to age from the North American Research Committee on Multiple Sclerosis** *(adapted figure)*.

## Methods

- Data was obtained from the Women's Health Initiative database. The Women's Health Initiative (WHI) enrolled a total of 161,808 women, with 93,676 participants in an observational study (WHI-OS) and 68,132 participants in clinical trials (WHI-CT), between 1993 and 1998 with an average of 7.6 years of follow-up until March 31, 2005. At baseline, the mean age was 63 years and about 18% of the women were from ethnic minority groups. Both multiple sclerosis and osteoporosis were diagnoses identified at baseline and in follow-up in the WHI cohort.
- The sample included 449 women who reported an MS diagnosis at baseline and 152,432 women without MS who comprised a control group. Baseline measures of self-reported osteoporosis, age, smoking status, steroid and anti-inflammatory use, and supplementary as well as dietary calcium and vitamin D were analyzed using multivariate linear regression.
- For both the MS and control groups, participants with osteoporosis at baseline were removed to monitor the time to incident osteoporosis.
- Variables having significant associations with MS and osteoporosis were monitored in follow-up and proportional hazards modeling was performed to adjust for relevant covariates over time and potential impact on incident cases of osteoporosis.
- Latency to incident osteoporosis and use of osteoporosis-related medications was also compared between MS and non-MS participants using either a T test or a Wilcoxian Ranksum test. The type of intervention for treating osteoporosis in both cohorts was also studied using a 2 x 2 contingency table analysis with a Fisher's exact test.

## Results

| | % (N) of MS / no-MS group | | |
|---|---|---|---|
| **Characteristic** | **MS (N=449)** | **No MS (N=152432)** | **p-value** |
| Self-report of osteoporosis diagnosis | 20.94 (94) | 7.7 (11762) | <0.0001 |
| Age stratum at randomization or enrollment: | | | <0.0001 |
| 50 – 54 | 21.6 (97) | 12.9 (19669) | |
| 55 – 59 | 26.1 (117) | 19.5 (29687) | |
| 60 – 69 | 40.8 (183) | 45.1 (68520) | |
| 70 – 79 | 11.6 (52) | 22.4 (34107) | |
| Smoking: | | | <0.0001 |
| Never | 38.8 (172) | 51.0 (76555) | |
| Past | 51.9 (230) | 42.1 (63201) | |
| Current | 9.3 (41) | 6.9 (10371) | |
| Steroid use | 0.9 (4) | 0.9 (1940) | 0.8020 |
| Anti-inflammatory use | 20.9 (94) | 19.1 (29044) | 0.3361 |
| Supplemental calcium: | | | 0.0331 |
| None | 44.3 (199) | 43.6 (66199) | |
| 1st quartile | 16.7 (75) | 16.8 (25478) | |
| 2nd quartile | 15.4 (69) | 11.8 (18001) | |
| 3rd quartile | 9.6 (43) | 13.8 (20935) | |
| 4th quartile | 14.0 (63) | 14.1 (21369) | |
| Dietary calcium: | | | 0.7445 |
| 1st quartile | 25.7 (115) | 25.0 (37935) | |
| 2nd quartile | 26.1 (117) | 25.0 (37932) | |
| 3rd quartile | 25.5 (114) | 15.0 (37935) | |
| 4th quartile | 22.8 (102) | 25.0 (37947) | |
| Supplemental Vit D: | | | 0.5219 |
| None | 53.9 (242) | 51.4 (78052) | |
| < 10 mcg | 8.7 (39) | 10.2 (15503) | |
| 10 mcg | 28.7 (129) | 28.5 (43368) | |
| >10 mcg | 8.7 (39) | 9.9 (15059) | |
| Dietary Vit D: | | | 0.1082 |
| 1st quartile | 29.5 (132) | 25.0 (37918) | |
| 2nd quartile | 22.1 (99) | 25.0 (27950) | |
| 3rd quartile | 25.7 (115) | 25.0 (37934) | |
| 4th quartile | 22.8 (102) | 25.0 (37947) | |

**Table 1**: **Baseline characteristics of participants with and without MS.** Women with MS are nearly three times as likely to report osteoporosis, are younger, are more likely to have smoked, and consume less supplemental calcium.

| Predictor: | Adjusted odds ratio (95% CI) | p-value |
|---|---|---|
| Multiple sclerosis | 4.14 (3.25, 5.27) | <0.0001 |
| Age stratum: | | <0.0001 |
| 50 – 54 | Reference | |
| 55 – 59 | 1.42 (1.28, 1.56) | |
| 60 – 69 | 2.67 (2.45, 2.91) | |
| 70 – 79 | 4.63 (4.24, 5.06) | |
| Smoking: | | 0.0003 |
| Never | Reference | |
| Past | 1.01 (0.97, 1.05) | |
| Current | 1.18 (1.09, 1.28) | |
| Steroid use | 2.88 (2.51, 3.30) | <0.0001 |
| Anti-inflammatory use | 1.35 (1.29, 1.41) | <0.0001 |
| Supplemental calcium: | | <0.0001 |
| None | Reference | |
| 1st quartile | 1.05 (0.97, 1.13) | |
| 2nd quartile | 1.56 (1.45, 1.68) | |
| 3rd quartile | 2.15 (2.00, 2.31) | |
| 4th quartile | 2.93 (2.75, 3.12) | |
| Dietary calcium: | | 0.0915 |
| Supplemental Vit D: | | <0.0001 |
| None | Reference | |
| <10mcg | 1.32 (1.23, 1.42) | |
| 10mcg | 1.06 (1.00, 1.13) | |
| >10mcg | 1.37 (1.28, 1.47) | |
| Dietary Vit D: | | <0.0001 |
| 1st quartile | Reference | |
| 2nd quartile | 0.92 (0.87, 0.98) | |
| 3rd quartile | 0.95 (0.89, 1.02) | |
| 4th quartile | 1.10 (1.02, 1.19) | |

**Table 2**: **Multivariate logistic regression model for self-report of an osteoporosis diagnosis.** A cross-sectional logistic regression of baseline data was performed to determine factors positively associated with an osteoporosis diagnosis . While this analysis cannot determine temporal ordering of predictors and osteoporosis, significant associations were observed with age, smoking, steroid use, anti-inflammatory use, supplemental calcium and vitamin D as well as dietary vitamin D. After adjusting for confounders, self-reported MS diagnosis was more strongly associated with self-reported osteoporosis diagnosis.

| Condition | Variable(s) | P-value |
|---|---|---|
| MS and osteoporosis | Age, educational level, smoking, BMI, recreational activity | <0.05 |
| MS | Moderate activity | <0.05 |
| | Hormones | 0.10 |
| | Menopausal age | 0.06 |
| | Steroid use | 0.24 |
| | Dietary calcium (mg) | 0.11 |
| | Dietary vitamin D (mcg) | 0.06 |
| Osteoporosis | Hormones, ethnicity, dietary and supplemental calcium and vitamin D, steroid and NSAID use | <0.05 |

**Table 3. WHI study follow-up.** Significant associations were found between variables and both MS and osteoporosis.

| Parameter | Hazard Ratio | 95% Hazard Ratio Confidence Limits | |
|---|---|---|---|
| Reporting MS at baseline | 1.166 | 0.936 | 1.452 |
| Hormones ever | 1.012 | 0.987 | 1.039 |
| Education level | 1.006 | 0.992 | 1.020 |
| Participant age | 0.998 | 0.997 | 1.000 |
| BMI | 1.001 | 0.999 | 1.003 |
| Dietary Calcium (mg) | 1.000 | 0.985 | 1.016 |
| Dietary Vitamin D (mcg) | 1.002 | 0.987 | 1.017 |
| Recreational activity (mins/wk) | 0.998 | 0.988 | 1.009 |
| Smoked at least 100 cigarettes ever | 0.994 | 0.971 | 1.018 |
| Taking steroids at year 3 visit | 1.047 | 0.935 | 1.173 |

**Table 4: Proportional hazards model of MS and follow-up variables on incident osteoporosis.** When adjusting for associations between follow-up variables and MS and/or osteoporosis, there is no significantly increased risk of developing osteoporosis for those with MS at baseline compared to those without.

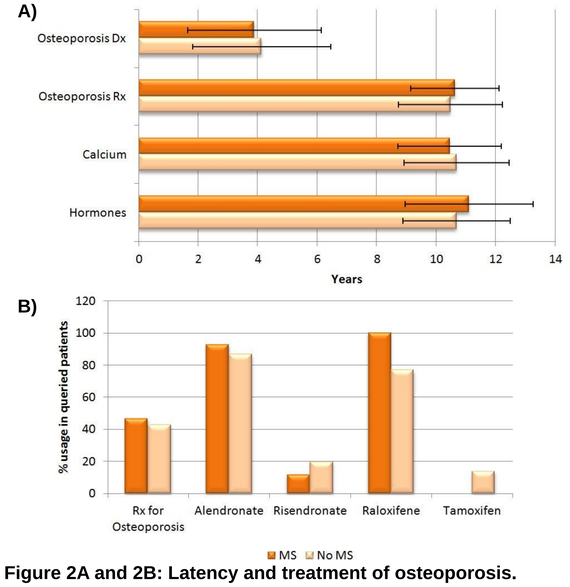


**Figure 2A and 2B: Latency and treatment of osteoporosis.**

A) No significant difference was observed between MS and non-MS participants in time to incident osteoporosis. Time to intervention with bisphosphonates, selective estrogen receptor modulators (SERMs), calcium, or hormones was similar between cohorts.

B) For management of osteoporosis in addition to calcium and vitamin D, most participants in both groups were on a bisphosphonate (alendronate > risendronate) and a SERM (raloxifene > tamoxifen).

## Conclusions

- Report of MS at baseline is significantly associated with report of osteoporosis at baseline (p<0.0001).
  - Associations were noted between MS and younger age, smoking history and less supplemental calcium.
  - Multivariate linear regression demonstrated a four-fold risk of baseline MS in association with osteoporosis when adjusting for age, smoking status, steroids and anti-inflammatory use, as well as dietary and supplemental calcium and vitamin D.
- WHI follow-up data demonstrated strong associations between:
  - MS and age, education, BMI, smoking, steroid use, dietary calcium and vitamin D, hormone use, moderate and recreational exercise, and menopausal age.
  - Osteoporosis and age, education, ethnicity, BMI, smoking, steroid and anti-inflammatory use, dietary and supplemental calcium and vitamin D, hormone use, and recreational exercise.
- However, when adjusting for these associations in proportional hazards modeling, MS at baseline was not significantly related to the report of osteoporosis at the end of the WHI study (p=0.88).
- Osteoporosis in the MS and non-MS populations presented with similar latencies and treatment for both groups was similar in terms of timing and type of intervention.
- The higher prevalence of osteoporosis at baseline suggests MS may significantly increase the risk of osteoporosis in premenopausal women while pharmacologic and lifestyle variables have a more significant role in post-menopausal women.
  - Postmenopausal women with MS may have less active inflammation and more slowly progressive accumulation of disability due to a proved neuro-degenerative process. With the three-fold risk noted in the WHI sample, the impact of MS on developing osteoporosis may be a function of early-stage MS, which was not prevalent in the WHI cohort.
  - Additional prospective studies should examine bone changes and incident osteoporosis in a younger MS population to determine if early detection and treatment could ultimately prevent the increased risk of osteoporosis seen in women with MS in this study.

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