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Christopher Perrone

*University of Massachusetts Medical School, Chrisp429@gmail.com*

Christine M. Foley


*University of Massachusetts Medical School, christine.foley@umassmed.edu*

Linda C. Churchill

*University of Massachusetts Medical School, Linda.Churchill@umassmed.edu*

*See next page for additional authors*

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

## **Authors**

Christopher Perrone, Christine M. Foley, Linda C. Churchill, Sybil L. Crawford, Judith K. Ockene, and Carolina Ionete

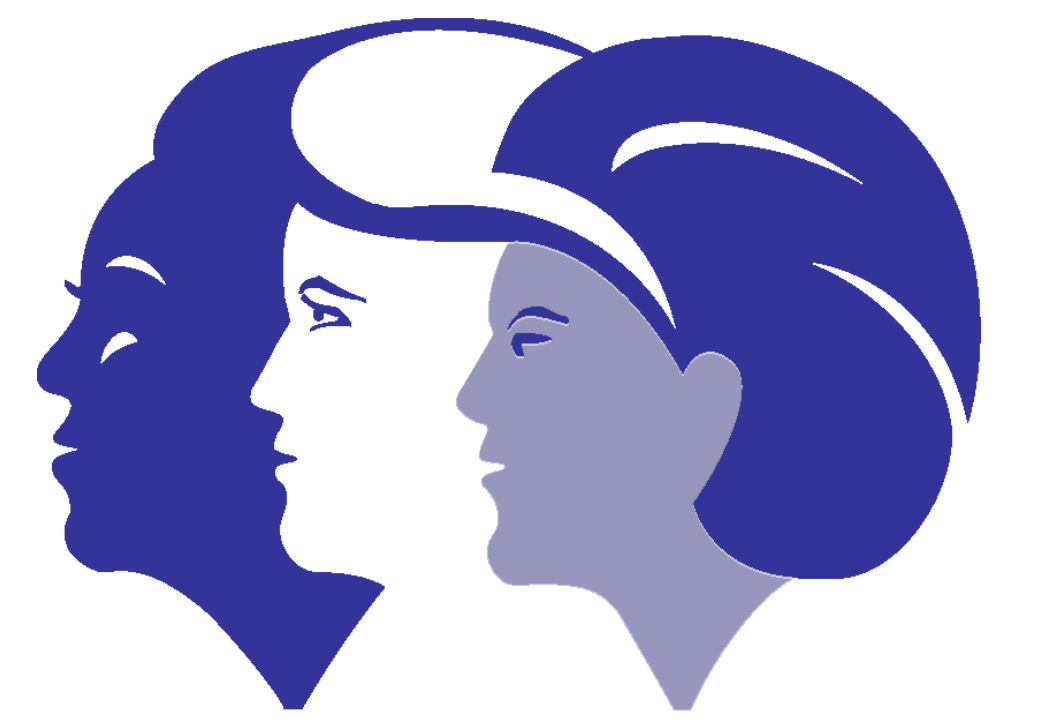
## **Keywords**

Multiple Sclerosis, Risk factors, Osteoporosis, Women's Health Initiative

## **Comments**

Poster presented on Senior Scholars Program Poster Presentation Day at the University of Massachusetts Medical School, Worcester, MA, on April 30, 2014. Medical student Christopher Perrone participated in this study as part of the Senior Scholars research program at the University of Massachusetts Medical School.





## 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.<sup>1,2</sup> Moreover, many patients with MS and low bone mass or previous fractures are not taking supplemental calcium or vitamin D.<sup>3</sup>
- 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.<sup>3-7</sup> 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.

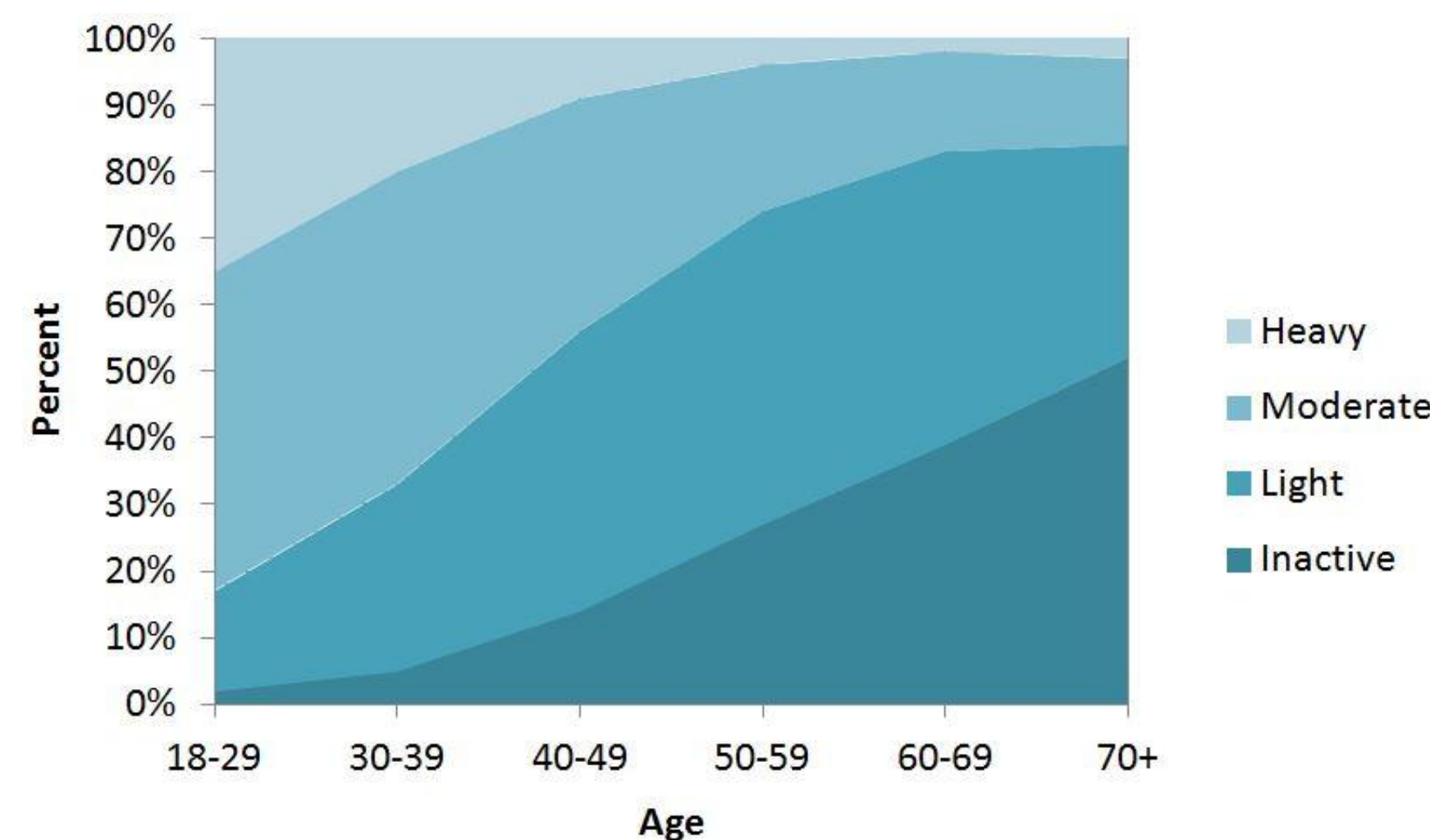


Figure 1: Activity level according to age from the North American Research Committee on Multiple Sclerosis (adapted figure).

## 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 Wilcoxon 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

Characteristic	% (N) of MS / no-MS group		p-value
	MS (N=449)	No MS (N=152432)	
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)	
1 <sup>st</sup> quartile	16.7 (75)	16.8 (25478)	
2 <sup>nd</sup> quartile	15.4 (69)	11.8 (18001)	
3 <sup>rd</sup> quartile	9.6 (43)	13.8 (20935)	
4 <sup>th</sup> quartile	14.0 (63)	14.1 (21369)	
Dietary calcium:			0.7445
1 <sup>st</sup> quartile	25.7 (115)	25.0 (37935)	
2 <sup>nd</sup> quartile	26.1 (117)	25.0 (37932)	
3 <sup>rd</sup> quartile	25.5 (114)	15.0 (37935)	
4 <sup>th</sup> 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
1 <sup>st</sup> quartile	29.5 (132)	25.0 (37918)	
2 <sup>nd</sup> quartile	22.1 (99)	25.0 (27950)	
3 <sup>rd</sup> quartile	25.7 (115)	25.0 (37934)	
4 <sup>th</sup> 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	
1 <sup>st</sup> quartile	1.05 (0.97, 1.13)	
2 <sup>nd</sup> quartile	1.56 (1.45, 1.68)	
3 <sup>rd</sup> quartile	2.15 (2.00, 2.31)	
4 <sup>th</sup> 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
1 <sup>st</sup> quartile	Reference	
2 <sup>nd</sup> quartile	0.92 (0.87, 0.98)	
3 <sup>rd</sup> quartile	0.95 (0.89, 1.02)	
4 <sup>th</sup> 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
	Moderate activity	<0.05
	Hormones	0.10
	Menopausal age	0.06
Osteoporosis	Steroid use	0.24
	Dietary calcium (mg)	0.11
	Dietary vitamin D (mcg)	0.06
	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.

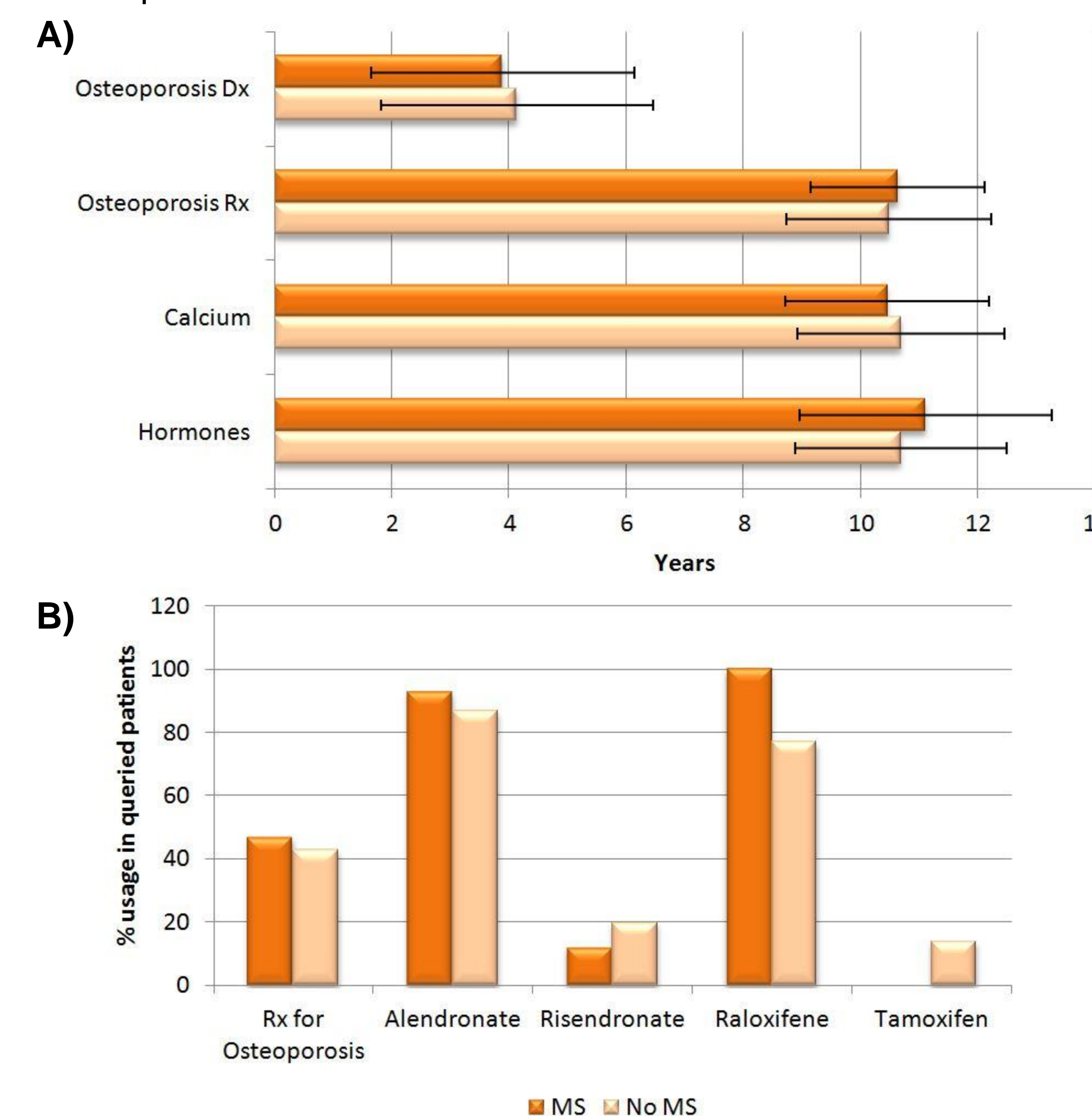


Figure 2A and 2B: Latency and treatment of osteoporosis. A) No significant difference was observed between MS and non-MS participants in time to incident osteoporosis. Time to intervention with bisphosphonates, selective estrogen receptor modulators (SERMs), calcium, or hormones was similar between cohorts. 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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