

SIG

THE ASSOCIATION BETWEEN MULTIPLE SCLEROSIS, FALLS, AND FRACTURE*

*DATA ARE PRELIMINARY AND SUBJECT TO CHANGE

Nicole C. Wright, Kathryn C. Fitzgerald, Jane A. Cauley, Ellen
M, Mowry, Carolyn J. Crandall

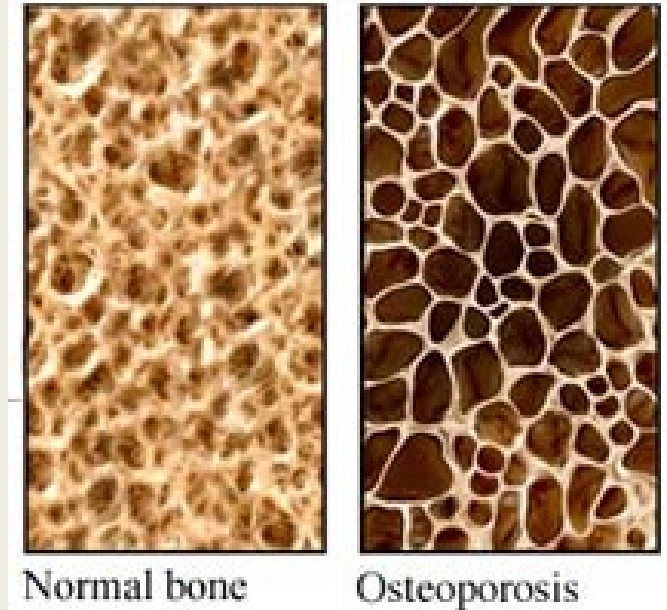
Women's Health Initiative Annual Meeting

May 3, 2019



Osteoporosis

- Is characterized by low bone mineral density (BMD) and structural deterioration
- Affects ~11 million adults over the age of 50 years in the United States
 - 8 million are women
- Leads to bone fragility and an increased susceptibility to fractures
- A woman's annual lifetime risk of hip fracture is equal to that of breast cancer, ovarian cancer, and uterine cancer combined



Normal bone

Osteoporosis



Fracture Risk Prediction Tools

FRAX	FORE FRC	ABH FRC	Garvan	QFracture
Age	Age	Age	Age	Age
Sex	Sex	Sex	Sex	Sex
Previous Fracture	Previous Fracture	Previous Fracture	Previous Fracture	Previous Fracture

<https://www.sheffield.ac.uk/FRAX/>

<https://riskcalculator.fore.org/default.aspx>

<https://americanbonehealth.org/calculator/>

<https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/>

<https://qfracture.org/>

Fracture Risk Prediction Tools

FRAX	FORE FRC	ABH FRC	Garvan	QFracture
Age	Age	Age	Age	Age
Sex	Sex	Sex	Sex	Sex
Previous Fx	Previous Fx	Previous Fx	Previous Fx	Previous Fx
Race/Ethnicity	Race/Ethnicity	Race/Ethnicity		Race/Ethnicity
Weight	Weight	Weight		Weight
Height	Height	Height		Height
Parental Hip Fx	Parental Hip Fx	Parental Hip Fx		Parental Hip Fx
Current Smoking	Current Smoking	Current Smoking		Smoking status
Alcohol	Alcohol	Alcohol		Alcohol status
Glucocorticoids	Glucocorticoids	Glucocorticoids		Glucocorticoids
RA	RA	RA		RA
Secondary OP	Secondary OP	Secondary OP		Secondary OP



Fracture Risk Prediction Tools

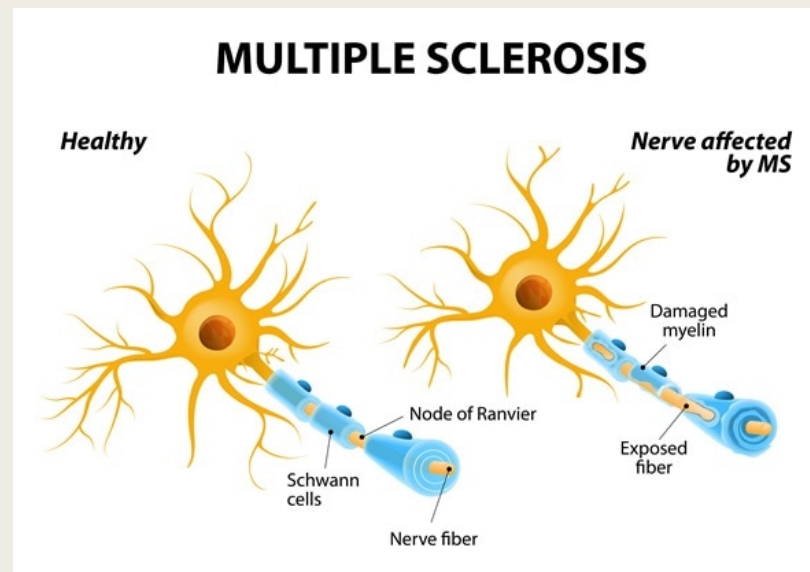
FRAX	FORE FRC	ABH FRC	Garvan	QFracture
	FN T-score	FN T-score	FN T-score	
FN BMD			FN BMD	
	DXA Machine Type		DXA Machine Type	
		Diabetes		Diabetes
		Cancer		Cancer
	OP Rx	OP Rx		
			# Falls over 12 months	H/o Falls





Multiple Sclerosis

- Central nervous system demyelinating disease characterized by episodic periods of inflammation followed by chronic neurologic dysfunction
- Affects >2 million people worldwide
- One of the most common causes of neurological disability in young adults





MS & Fracture

■ MS patients have an increased risk for fracture

- Canada: 67% increase in major osteoporotic fractures

J Bone Miner Res. 2019 Jan 28:e3682

- Netherlands: 1.7 fold increase risk of osteoporotic fractures; 4-fold increased risk of hip fractures

Neurology. 2012 Jun 12;78(24):1967-73

- Finland: 50% increase in all op fractures; 5-fold increase and 2.4-fold increase in hip and humerus fractures

Acta Neurol Scand. 2017 May;135(5):516-521

- Denmark: 90% increased risk of femur/hip fractures

Mult Scler. 2012 Nov;18(11):1609-16

- USA: Prevalence of MS in hip fractures was double than predicted

Journal of Multidisciplinary Healthcare, vol. 7, pp. 119–122, 2014.



Calculating Fracture Risk in MS Patients

- Using GPRD data, researchers in the UK developed a fracture risk score specific to MS patients to predict 5- and 10-year fracture outcomes
 - However, the mean age of the study sample was 44.5 years, and only 13.2% was 60+
- Little is known about the relationship between MS and fracture in a postmenopausal population
- Likewise, most studies have utilized national registries and/or administrative data, not allowing for the adjustment of lifestyle variables
- The WHI population presents a unique opportunity to study women with long-standing MS and provide valuable information characterizing fracture risk in an older population of MS women



Study Objectives

1. Examine whether multiple sclerosis is independently associated with **falls** risk
2. Examine whether multiple sclerosis is independently associated with **fracture** risk
3. Assess the utility of FRAX (without BMD) and the MS-specific fracture risk tool in predicting fracture in postmenopausal women with MS



Methods

■ Sample:

- WHI CT and OS cohorts (N = 151,406)

■ Exposure - MS:

- Self-reported at baseline

■ Outcomes - Falls:

- Prospectively collected using questionnaires
- Number of times the participant fell (excluding falls to sports) in the interval since medical history update

■ Fractures:

- Prospectively collected using questionnaires
- Sites of Interest:
 - Hip, Clinical vertebral
 - Upper limb (hand, wrist, humerus, shoulder, clavicle)
 - Lower limb (femur, patella, tib/fib, ankle, foot)
 - Total

■ Exclusions:

- Those without follow-up data (n=877)
- Missing MS data (n=9,375)
- Missing falls data (n=1080)



Methods – Is MS independently Associated with Falls and Fracture?

■ Falls

- Event defined as ≥ 2 falls in the past year
- Used a generalized estimating equation model with a logistic link to estimate the association between MS and falls with and without adjustment

■ Fractures

- Used Cox-proportional hazard models to assess the relationship between MS and time to first fracture with and without adjustment
 - Duration of follow-up will be defined as time to first fracture, otherwise, duration of follow-up will be defined as the minimum of time until last follow-up visit, or death
- Individual regression models for each anatomical fracture site



MS Fracture Risk Score

- Based on 1987-2009 UK GPRD and 1997-2008 Hospital Episode Statistics (HES) data
- MS defined using validated algorithms
- Fracture outcomes:
 - All fractures
 - clinical osteoporotic fracture

	OP Fx	Hip Fx
MS	4	13
Female	3	2
Age (for every 10 y)	5	11
Use of PO/IV glucocorticoids*	1	3
Use of antidepressants*	1	3
Use of anticonvulsants*	6	
History of falling 3 mo – 1 y before	4	6
History of fracture	4	
History of fatigue*		18
Current smoker	2	4
BMI <20 kg/m ²	2	7
BMI >25 kg/m ²	- 1	- 6
* In the prior 6 months		



Operationalizing MS Fracture Risk Score in the WHI

- Use at baseline:
 - Glucocorticoids
 - Antidepressants
 - Anticonvulsants
- History of fatigue in prior 6 months:
 - **Variable ENERFAT - Form 36/37: Thoughts & Feelings:** questions
 - 76 – Did you feel full of pep?
 - 80 – Did you have a lot of energy?
 - 82 – Did you feel worn out?
 - 84 – Did you feel tired?
 - Scores ≤ 45 have been established as representing clinically significant fatigue J Pain Symptom Manage 36(5):480– 487

Characteristics by MS Status



	No MS (N = 150,961)	MS (N=445)	P-value
Age (mean, SD)	63.3 (7.2)	60.6 (6.6)	<0.001
Race/Ethnicity			0.016
NH-White	124,785 (82.9)	370 (83.3)	
Black	13,575 (9.0)	43 (9.7)	
Hispanic	5,782 (3.8)	15 (3.4)	
Other	6,451 (4.3)	16 (3.6)	
College Grad+	59,599 (39.8)	191 (43.2)	0.007
<2.5 Physical Activity (MET hrs/wk)	38,236 (25.4)	156 (35.1)	<0.001
Current Smokers	10,248 (6.9)	41 (9.3)	<0.001
Current HT User	61,035 (40.5)	207 (46.5)	0.030
Anti-Depressant Use	10,773 (7.1)	67 (15.1)	<0.001
Anti-Anxiety Use	4,791 (3.2)	25 (5.6)	0.003
Hypnotics Use	4,210 (2.8)	25 (5.6)	<0.001
Fracture at Age 55+	19,528 (13.9)	97 (23.3)	<0.001
Fair/Poor General Health	13,556 (9.0)	83 (18.7)	<0.001



Outcomes by MS Status

	No MS (N = 150,961)	MS (N = 445)	P-value
≥ 2 Falls	46,147 (30.6)	257 (57.8)	<0.001
Fractures			
Hip	6,510 (4.3)	24 (5.4)	0.263
Upper Limb	20,604 (13.6)	75 (16.9)	0.049
Central Body	16,780 (11.1)	59 (13.3)	0.151
Total Fracture	55,730 (36.9)	196 (44.0)	0.002



Is MS Independently Associated with Falls?

	No	Yes OR (95% CI)
Base	1.0 (Ref)	3.87 (3.31, 4.52)

Base: OS/CT, HT treatment arm

Model 1: Base + age

Model 2: 1 + demographics (race/ethnicity and education)

Model 3: 2 + lifestyle (general health, physical activity, smoking status)

Model 4: 3 + medications (HT, anti-depressants, anti-anxiety, narcotics)



Is MS Independently Associated with Falls?

	No	Yes OR (95% CI)
Base	1.0 (Ref)	3.87 (3.31, 4.52)
Model 1	1.0 (Ref)	4.09 (3.49, 4.79)
Model 2	1.0 (Ref)	4.03 (3.44, 4.73)

Base: OS/CT, HT treatment arm

Model 1: Base + age

Model 2: 1 + demographics (race/ethnicity and education)

Model 3: 2 + lifestyle (general health, physical activity, smoking status)

Model 4: 3 + medications (HT, anti-depressants, anti-anxiety, narcotics)



Is MS Independently Associated with Falls?

	No	Yes OR (95% CI)
Base	1.0 (Ref)	3.87 (3.31, 4.52)
Model 1	1.0 (Ref)	4.09 (3.49, 4.79)
Model 2	1.0 (Ref)	4.03 (3.44, 4.73)
Model 3	1.0 (Ref)	3.42 (2.91, 4.01)
Model 4	1.0 (Ref)	3.31 (2.81, 3.90)

Base: OS/CT, HT treatment arm

Model 1: Base + age

Model 2: 1 + demographics (race/ethnicity and education)

Model 3: 2 + lifestyle (general health, physical activity, smoking status)

Model 4: 3 + medications (HT, anti-depressants, anti-anxiety, narcotics)



Is MS independently Associated with Fracture?

	Hip	Upper Limb	Lower Limb	Central Body	Total
Base	1.23 (0.83, 1.84)	1.24 (0.99, 1.55)	1.39 (1.12, 1.73)	1.20 (0.93, 1.54)	1.29 (1.13, 1.49)

Base: OS/CT, HT treatment arm; Model 1: Base + age; Model 2: 1 + demographics (race/ethnicity and education); Model 3: 2 + lifestyle (general health, physical activity, smoking status); Model 4: 3 + medications (HT, anti-depressants, anti-anxiety, narcotics)



Is MS independently Associated with Fractures?

	Hip	Upper Limb	Lower Limb	Central Body	Total
Base	1.23 (0.83, 1.84)	1.24 (0.99, 1.55)	1.39 (1.12, 1.73)	1.20 (0.93, 1.54)	1.29 (1.13, 1.49)
Model 1	1.77 (1.18, 2.64)	1.36 (1.09, 1.71)	1.42 (1.14, 1.77)	1.57 (1.22, 2.03)	1.42 (1.23, 1.63)
Model 2	1.79 (1.20, 2.67)	1.37 (1.09, 1.71)	1.40 (1.13, 1.75)	1.58 (1.22, 2.04)	1.41 (1.23, 1.62)

Base: OS/CT, HT treatment arm; Model 1: Base + age; Model 2: 1 + demographics (race/ethnicity and education); Model 3: 2 + lifestyle (general health, physical activity, smoking status); Model 4: 3 + medications (HT, anti-depressants, anti-anxiety, narcotics)

Is MS independently Associated with Fractures?



	Hip	Upper Limb	Lower Limb	Central Body	Total
Base	1.23 (0.83, 1.84)	1.24 (0.99, 1.55)	1.39 (1.12, 1.73)	1.20 (0.93, 1.54)	1.29 (1.13, 1.49)
Model 1	1.77 (1.18, 2.64)	1.36 (1.09, 1.71)	1.42 (1.14, 1.77)	1.57 (1.22, 2.03)	1.42 (1.23, 1.63)
Model 2	1.79 (1.20, 2.67)	1.37 (1.09, 1.71)	1.40 (1.13, 1.75)	1.58 (1.22, 2.04)	1.41 (1.23, 1.62)
Model 3	1.59 (1.05, 2.39)	1.33 (1.06, 1.67)	1.34 (1.07, 1.66)	1.41 (1.08, 1.83)	1.32 (1.15, 1.52)
Model 4	1.54 (1.02, 2.31)	1.32 (1.05, 1.66)	1.32 (1.06, 1.65)	1.37 (1.05, 1.78)	1.30 (1.13, 1.50)

Base: OS/CT, HT treatment arm; Model 1: Base + age; Model 2: 1 + demographics (race/ethnicity and education); Model 3: 2 + lifestyle (general health, physical activity, smoking status); Model 4: 3 + medications (HT, anti-depressants, anti-anxiety, narcotics)



Assessing the utility of fracture risk tools in postmenopausal women with MS

	No MS (N = 150,961)	MS (N=445)
FRAX Score , mean (SD)	10.3 (6.9)	9.3 (6.3)
FRAX MOF $\geq 20\%$, N (%)	13,048 (8.6)	31 (7.0)
FRAX Hip $\geq 3\%$, N (%)	32,482 (21.5)	70 (15.7)
Energy/Fatigue Construct , mean (SD)	63.4 (19.2)	53.4 (22.7)
Energy/Fatigue ≤ 45 , N (%)	27,985 (18.8)	165 (37.7)
MS OP Fx Score , mean (SD)	35.0 (4.9)	49.2 (4.8)
MS Hip Fx Score , mean (SD)	68.9 (11.5)	84.6 (12.1)



Fracture Risk Score by Age - FRAX

	MOF				Hip Fx		
	No MS (mean, SD)	MS (mean, SD)	P-value		No MS (mean, SD)	MS (mean, SD)	P-value
<55	4.2 (1.9)	4.4 (1.9)	0.147		0.26 (0.17)	0.29 (0.16)	0.046
55 - 59	6.5 (3.2)	7.6 (3.7)	<0.001		0.52 (0.42)	0.66 (0.57)	<0.001
60 - 64	9.1 (4.7)	9.0 (4.7)	0.858		1.1 (0.9)	1.2 (0.9)	0.197
65 - 69	11.9 (5.8)	13.1 (6.4)	0.082		2.3 (1.8)	2.8 (2.3)	0.019
70 - 74	15.3 (7.0)	18.1 (8.4)	0.010		4.8 (4.2)	6.0 (5.7)	0.063
≥ 75	20.3 (9.3)	13.1 (5.5)	0.038		9.1 (7.7)	4.7 (2.6)	0.132



Discussion

- Our results provide consistent evidence that women with MS have an increased odds of falls and an increased risk for fractures
- Our fracture risk estimates are not as large as other studies
 - Potentially due to age of participants
- On average, FRAX scores are lower in patients with MS
 - Potential to underestimate fractures in MS population
- However, we did observe significantly higher FRAX scores in younger age groups



Strengths & Limitations

Limitations

- **Self-report of MS**
 - 98.8% sensitive based on chart review or physician report
- **No information on MS duration or severity**
 - Potentially use question related to the use of assistive walking devices as a marker or severity
- **Very little information on MS medications**
 - No known relationship with bone; however, reduction in MS symptoms could reduce falls and subsequent fx

Strengths

- Available demographic and lifestyle data
- Long-term outcome follow-up
- Diverse cohort of postmenopausal women with MS



Summary

- Postmenopausal women with MS have:
 - 3.3-fold increased odds of having ≥ 2 falls
 - 30 – 54% increased risk of fractures
 - Lower FRAX scores on average than women without MS
 - Higher MS fracture risk score
 - Younger women with MS have significantly higher MOF and hip FRAX scores

Thank you!

