Figure e-1. Schematic of subjects meeting inclusion/exclusion criteria (N each)

MS CASES: 248

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ASSESSMENT, WHILE DIAGNOSED WITH MS, BETWEEN 3 AND 10 YEARS AFTER FINAL MENSTRUAL PERIOD: 147

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WELL-DEFINED MENOPAUSAL TYPE: 123
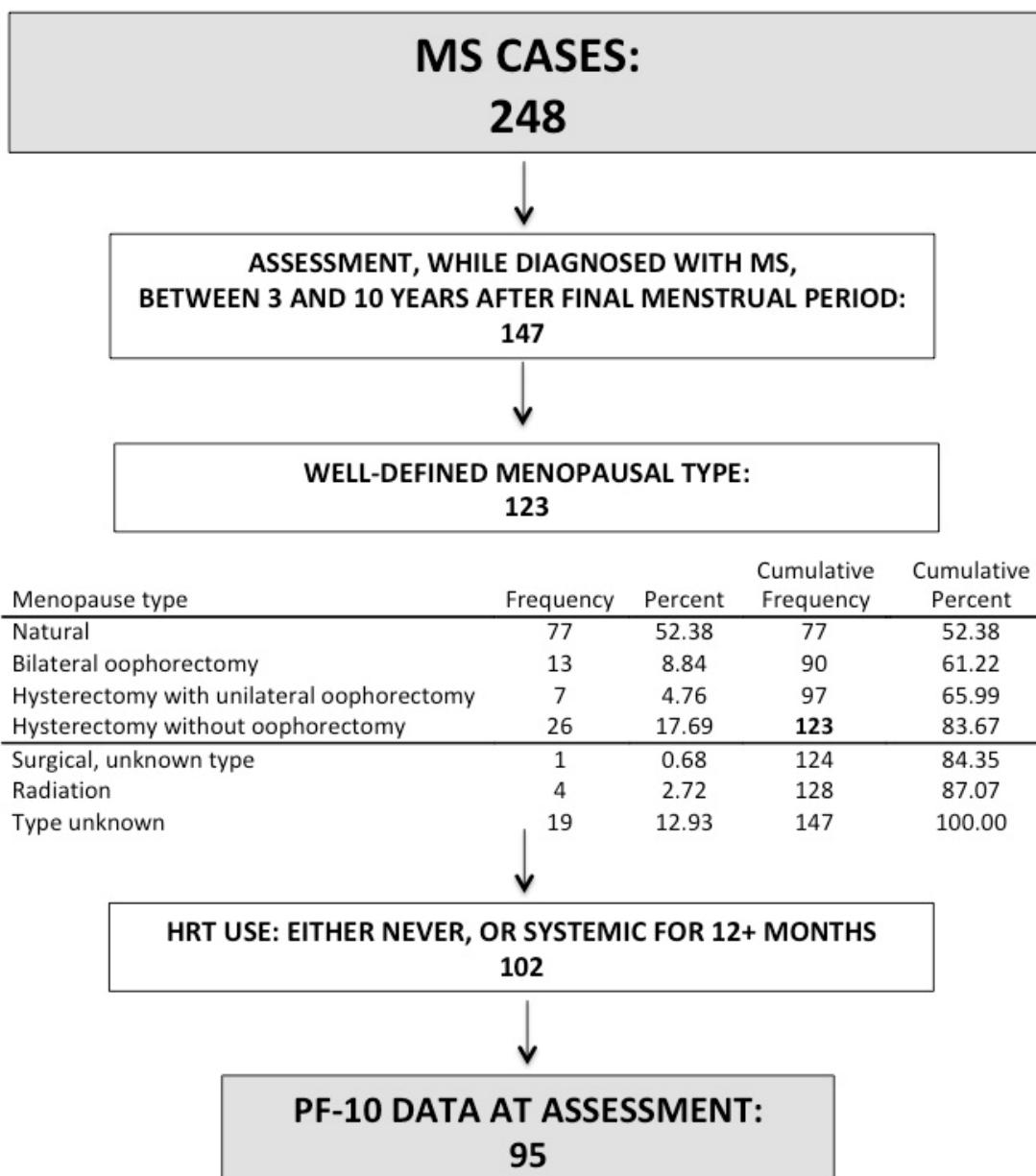
Menopause type	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Natural	77	52.38	77	52.38
Bilateral oophorectomy	13	8.84	90	61.22
Hysterectomy with unilateral oophorectomy	7	4.76	97	65.99
Hysterectomy without oophorectomy	26	17.69	**123**	83.67
Surgical, unknown type	1	0.68	124	84.35
Radiation	4	2.72	128	87.07
Type unknown	19	12.93	147	100.00

↓

HRT USE: EITHER NEVER, OR SYSTEMIC FOR 12+ MONTHS 102

↓

PF-10 DATA AT ASSESSMENT: 95

Variable		N	Mean	Miss
PF-10	physical functioning index (0-100)	95	48.25	7
BP	pain index (0-100)	77	65.88	25
GH	general health perceptions (0-100)	77	55.14	25
MCS	standarized mental health component scale	59	52.25	43
MH	mental health index (0-100)	77	75.14	25
PCS	standarized physical component scale	59	34.44	43
RE	role emotional (0-100)	77	71.87	25
RP	role physical (0-100)	77	39.61	25
SF	social functioning (0-100)	77	70.62	25
VT	vitality index (0-100)	77	44.28	25

Table e-1. Comparison of NHS subjects with MS with data fulfilling inclusion criteria and included in the PF10 analyses, versus individuals not in the PF10 analyses.

	Not included N=42-148	Included N=89-95	p-value	N=0	N=1
Age (years)*	56.1 (3.0)	56.5 (3.7)	0.49	52	95
BMI (kg/m^2)*	25.8 (5.0)	26.0 (5.2)	0.74	50	90
Smoking (pack-years)*	**18.0 (17.9)**	**11.6 (15.7)**	**0.03**	**52**	**93**
MS duration (years)*	9.4 (6.9)	9.2 (6.1)	0.89	52	95
BMI age 18 (kg/m^2)*	21.6 (3.0)	22.2 (3.2)	0.16	129	89
Vitamin D intake (IU/day)*	250.5 (361.9)	235.4 (248.4)	0.81	42	92
Ancestry					
Caucasian - other (%)	54.0	61.0	0.28	148	95
Southern European (%)	13.5	12.6	0.84	148	95
Scandinavian (%)	6.1	5.3	0.79	148	95
Other (%)	26.4	21.1	0.35	148	95
Latitude of residence at age 15					
North (%)	45.3	44.2	0.87	148	95
Middle (%)	37.2	40.0	0.66	148	95
South (%)	2.0	7.4	**0.04**	**148**	**95**
Missing (%)	15.5	8.4	0.1	148	95
Premenopausal physical activity (METs/week)	9.9 (12.6)	8.8 (11.2)	0.62	40	90
Time since menopause (years)	5.8 (1.8)	6.1 (1.9)	0.46	52	95
Menopause type					
Natural (%)	45.8	63.2	**0.008**	153	95
Bilateral oophorectomy (%)	21.6	10.5	**0.03**	**153**	**95**
Other surgical (unilateral/no oophorectomy) (%)	13.1	26.3	**0.009**	**153**	**95**
Current HT user**	62.5	64.2	0.88	24	95

*At first post-menopausal assessment. Values are means (SD) or percentages and are standardized to the age distribution of the study population.

**HT use was categorized as systemic, estrogen based, for at least 12 months, vs. never use.

Table e-2. Full set of outcomes and covariates

	PF		PCS		BP		GH		MH		RE		RP		SF		VT		MCS	
	N=95		N=59		N=77		N=77		N=77		N=77		N=77		N=77		N=77		N=59	
	β Est	p-value	β Est	p-value	β Est	p-value	β Est	p-value	β Est	p-value	β Est	p-value	β Est	p-value	β Est	p-value	β Est	p-value	β Est	p-value
HT USE*																				
age adjusted	17.8	**0.015**	6.2	0.08	-4.4	0.46	-2.4	0.69	-4.3	0.34	-11.4	0.22	0.7	0.94	6.5	0.36	3.2	0.57	-2.3	0.38
base	20.0	**0.01**	8.2	**0.04**	-5.8	0.35	-0.4	0.95	-6.1	0.22	-8.0	0.42	-0.6	0.95	6.0	0.42	1.1	0.85	-2.4	0.42
base + BMI	18.5	**0.02**	6.8	0.10	-9.2	0.14	-4.1	0.50	-6.7	0.19	-11.9	0.23	-8.2	0.43	1.1	0.88	-2.5	0.67	-3.0	0.33
base + packyears	21.8	**0.008**	8.4	**0.04**	-5.6	0.38	-3.4	0.60	-5.6	0.27	-6.4	0.53	1.2	0.92	5.7	0.46	-0.0	1.00	-3.0	0.35
base + ancestry	23.2	**0.004**	9.1	**0.02**	-3.7	0.56	0.8	0.90	-4.7	0.36	-4.5	0.65	5.1	0.65	10.8	0.15	3.9	0.53	-1.1	0.72
base + region	21.1	**0.009**	8.0	0.06	-6.7	0.29	1.3	0.84	-6.7	0.18	-5.2	0.60	1.1	0.93	7.5	0.33	2.2	0.73	-1.9	0.54
base + BMI18	20.0	**0.01**	8.1	0.05	-6.1	0.35	-1.0	0.87	-6.8	0.18	-9.2	0.36	-0.4	0.97	5.1	0.51	-0.3	0.96	-2.5	0.42
base + Vitamin d	21.2	**0.009**	9.7	**0.02**	-3.7	0.55	1.1	0.86	-5.4	0.28	-5.8	0.56	2.2	0.85	7.3	0.33	2.2	0.72	-3.1	0.30
base + METS	21.3	**0.01**	8.2	**0.05**	-6.2	0.33	0.1	0.98	-5.7	0.25	-9.1	0.36	-1.1	0.92	5.2	0.49	0.6	0.92	-3.5	0.24
HT DURATION**																				
age adjusted	0.2	**0.02**	0.1	0.07	0.02	0.77	0.03	0.65	-0.03	0.59	-0.1	0.39	0.003	0.98	0.07	0.44	0.02	0.79	-0.02	0.55
base	0.2	0.06	0.1	0.06	-0.01	0.89	0.02	0.80	-0.05	0.43	-0.1	0.50	-0.02	0.88	0.05	0.62	-0.04	0.64	0.00	0.95
base + BMI	0.2	0.10	0.1	0.16	-0.05	0.57	-0.02	0.81	-0.06	0.42	-0.1	0.32	-0.1	0.43	-0.01	0.95	-0.08	0.31	-0.01	0.82
base + packyears	0.2	**0.05**	0.1	0.10	-0.02	0.81	-0.03	0.75	-0.05	0.44	-0.08	0.56	0.00	1.00	0.02	0.82	-0.06	0.50	-0.01	0.90
base + ancestry	0.2	0.06	0.1	0.10	0.00	0.96	0.02	0.82	-0.03	0.64	-0.07	0.60	0.01	0.95	0.08	0.46	-0.02	0.79	0.02	0.73
base + region	0.2	**0.05**	0.1	0.13	-0.03	0.75	0.04	0.64	-0.07	0.31	-0.08	0.57	-0.01	0.93	0.05	0.61	-0.04	0.63	-0.01	0.90
base + BMI18	0.2	0.06	0.1	0.07	-0.01	0.89	0.02	0.83	-0.06	0.41	-0.10	0.48	-0.02	0.91	0.05	0.67	-0.05	0.56	0.00	0.96
base + Vitamin d	0.2	**0.05**	0.1	**0.05**	0.01	0.91	0.05	0.59	-0.04	0.58	-0.05	0.71	0.01	0.96	0.08	0.45	-0.02	0.79	0.00	0.99
base + METS	0.2	**0.05**	0.1	0.08	-0.02	0.86	0.03	0.70	-0.04	0.56	-0.09	0.53	-0.01	0.92	0.06	0.59	-0.03	0.74	-0.01	0.84

Base Model: Generalized linear regression adjusted for age, MS duration, time since menopause, and menopause type.
Additional models adjusted for BMI (body mass index), smoking (packyears), ancestry, latitude of residence at age 15, BMI at age 18, supplemental vitamin D intake, and METS.

SF-36 subscales: BP (bodily pain), GH (general health perceptions), MH (mental health), RE (emotional role functioning), RP (physical role functioning), SF (social role functioning), VT (vitality), PF (physical function), MCS (mental composite score), PCS (physical composite score).

* HT use was categorized as systemic, estrogen based, for at least 12 months, vs. never use. The estimate provided represents the increase in physical function measure observed if HT use = 1.
** HT use was measured continuously in months. The estimate provided represents the increase in physical function measure observed for each additional month of systemic, estrogen based, HT use. To obtain the estimate of effect over 1-year, multiply the beta-estimate by 12.

Table e-3. Association between HT use* and PF10 at first postmenopausal assessment in women without an MS diagnosis.

	NATURAL + SURGICAL MENOPAUSE		
	N	β Estimate	p-value
Model 1 (age-adjusted)	31,935	0.5	**0.02**
Model 2 (adjusted for age and menopausal factors)	31,935	1.0	**<.0001**
Model 3 (fully adjusted)	31,935	-0.8	**0.0003**

Models: Generalized linear regression.
      Model 1: adjusted for age.
      Model 2: adjusted for age, time since menopause, and menopause type (natural, bilateral oophorectomy, other surgical).
      Model 3: adjusted for Model 2 + *as well as:* ancestry, pack-years of smoking, vitamin D intake, BMI at PF10, BMI age 18, latitude age 15, and premenopausal physical activity.

* HT use was categorized as systemic, estrogen based, for at least 12 months, vs. never use. The estimate provided represents the increase in PF10 observed if HT use = 1.