

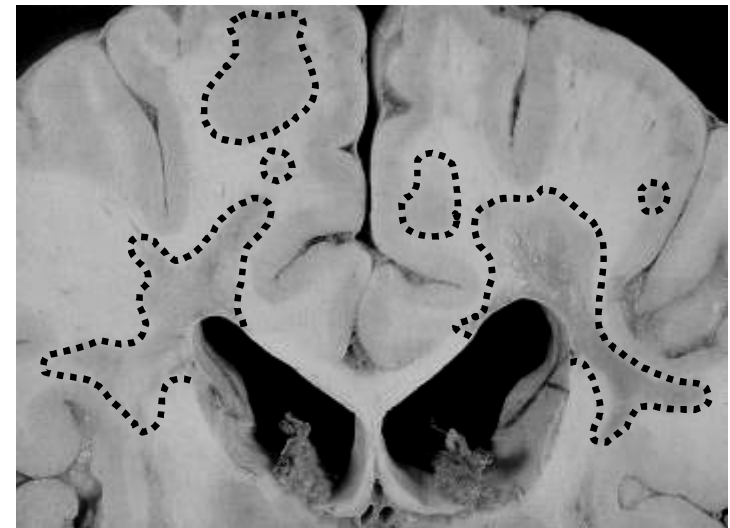
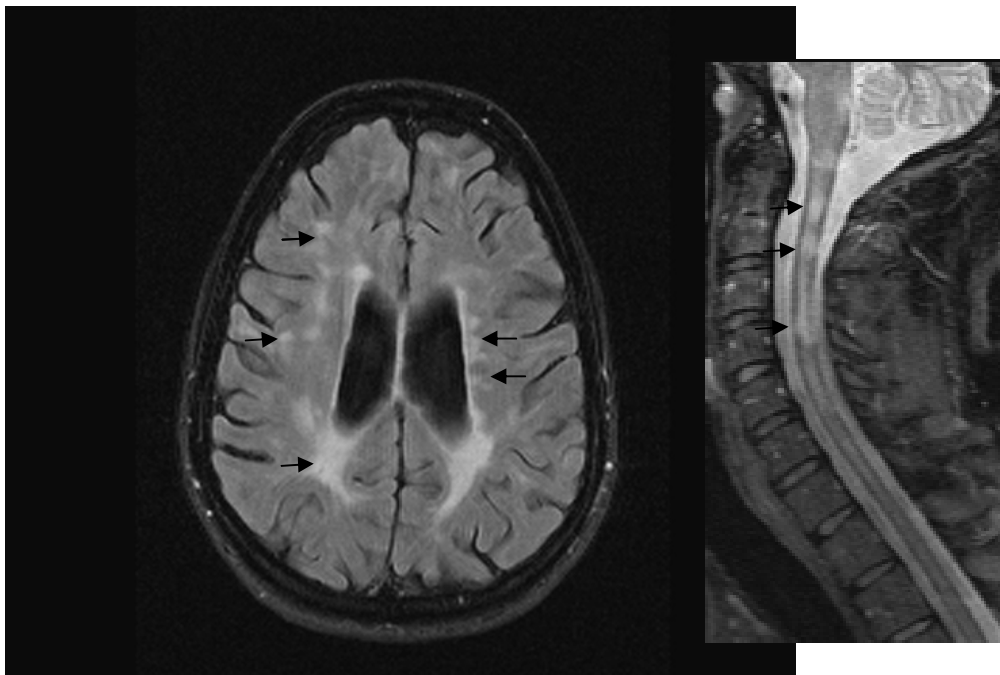
Sex Differences in Multiple Sclerosis: Clinical, Imaging, and Pathology

Sex Differences and Implications for
Translational Neuroscience Research – A Workshop
Forum on Neuroscience and Nervous System Disorders
Institute of Medicine of the National Academies

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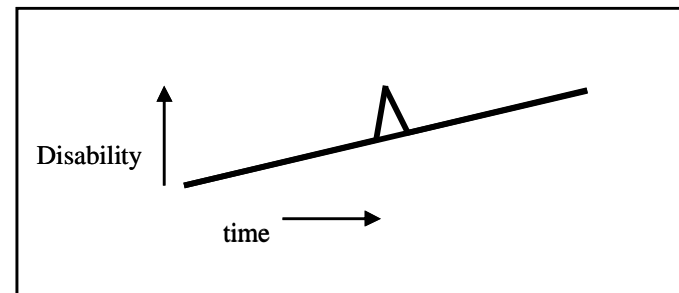
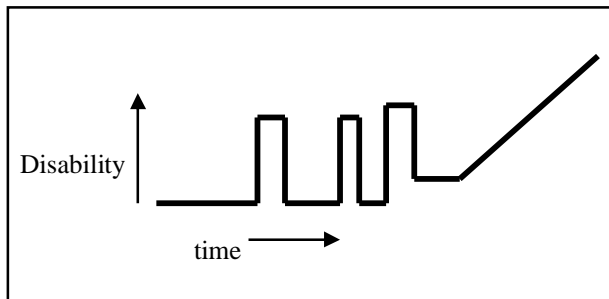
Multiple Sclerosis Background

- ◆ US prevalence approx 1/1000
- ◆ Typically diagnosed between the ages of 25-45
- ◆ The most common, non-traumatic cause of disability in young adults
- ◆ By 15 years from onset, ~ 75% have a progressive course and moderate-severe disability



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- ◆ By 15 years from onset, ~ 75% have a progressive course and moderate-severe disability
 - ◆ Relapsing-remitting (85%)
 - ◆ Secondary Progressive (SPMS; 75-80% of RRMS)
 - ◆ Primary Progressive (PPMS, 10%)
 - ◆ Progressive Relapsing (5%)



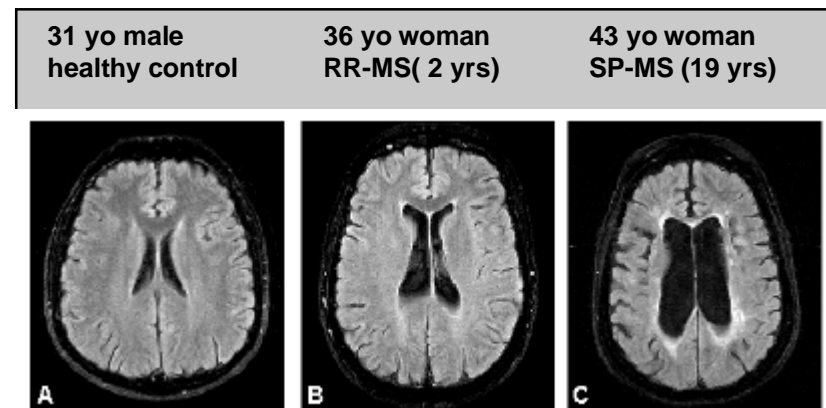
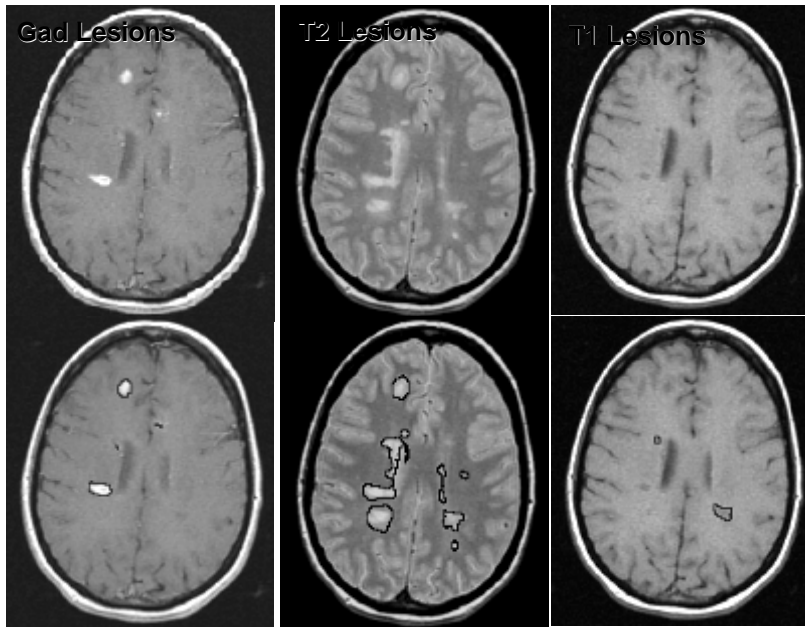
- ◆ Neuromyelitis optica: rare (~1%) CNS demyelinating disorder
 - Optic neuritis, transverse myelitis, atypical brain lesions

Multiple Sclerosis

Measuring Disease



- ◆ 2 categories of measuring MS:
- ◆ Active inflammation:
 - Clinical relapses
 - Gadolinium-enhancing lesions
- ◆ Accumulated injury
 - Disability progression
 - MRI lesion burden: T2 lesions, T1 lesions
 - Brain atrophy: whole brain, white matter, gray matter
 - Advanced imaging: magnetization transfer ratio, diffusion-weighted imaging



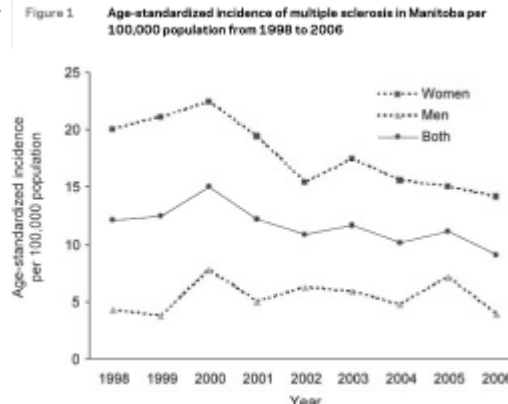
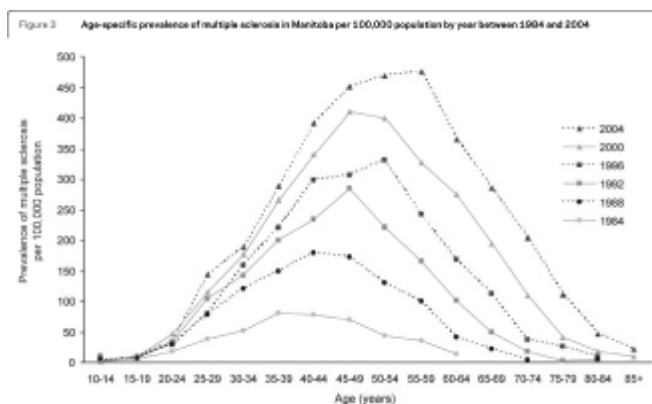
Multiple Sclerosis Sex Differences

Clinical Observations

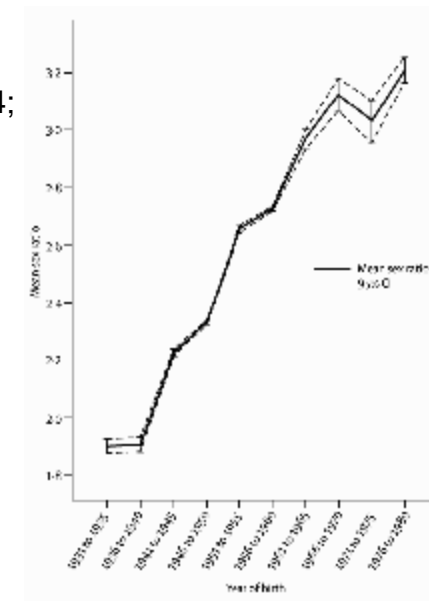
- ◆ 2-3x more common in women (Orton, Lancet Neurol 2006; Alonso, Neurol 2008; Debouverie, EJM 2008)
 - Ratio decreased with older age (Marrie, Neurol 2010)
 - Equal ratio among PPMS (Edan, JNS 2009)
- ◆ Neuromyelitis optica: >3 more common in women
- ◆ Peak incidence is earlier in women: 35-39 yrs; men: 45-49 yrs (Marrie, Neurol 2009)
 - Peak prevalence is similarly shifted – women: 45-59 yrs; men 55-69 yrs
- ◆ Prevalence is increasing
 - Incidence roughly stable
 - Less diagnostic delay and greater survival (Ekestern, EJM 2004; Bronnum-Hansen, Brain 2004; Marrie, Neurol 2005)

Age, y	Women:men	
	Rate ratio	95% CI
≤24*	7.07	3.95-12.6
25-29	3.52	2.33-5.31
30-34	4.09	2.72-6.14
35-39	4.31	3.04-6.10
40-44	3.61	2.57-5.06
45-49	2.56	1.81-3.62
50-54	2.16	1.45-3.22
55-59	1.90	1.17-3.09
60-64	1.42	0.74-2.74
≥65*	1.47	0.65-3.92
Total	3.15	2.75-3.60

Marrie, Neurol 2010



Marrie, Neurol 2010



Orton, Lancet Neurol 2006

Multiple Sclerosis Sex Differences

Clinical Observations

- ◆ Prognosis (relapses, progressive disability): variable observations
 - Females have favorable prognosis (Confavreux, Brain 1980; Detels, Arch Neurol 1982; Wolfson, Neuroepid. 1987; Weinschenker, Brain 1991; Runmarker, Brain 1993; Trojano, JNNP 1995; Kantarci, Neurol 1998; Confavreux, Brain 2003; Wolinsky, MS and Demyelinating Diseases [book] 2006; Khaleeli, Ann Neurol 2008)
 - No sex difference (Broman Acta Neurol Scand. 1981; Visscher Acta Neurol Scand. 1984; Riise Acta Neurol Scand 1992; Amato JNS 1999; Cotrell, Brain 1999; Bergamaschi Neuroepid. 2005; Tremlett, Neurol 2005).
 - No sex difference observed in neuromyelitis optica
- ◆ Relationship to sex hormones:
 - Decreased relapse rate during pregnancy – particularly during third trimester – then rebounding after pregnancy (Confavreux, NEJM 1998; Alonso, Arch Neurol 2005)
 - Effect of oral contraceptives:
 - ◆ Lower incidence of MS (Villard-Mackintosh, Contraception 1993; Alonso, Arch Neurol 2005)
 - ◆ No effect (Thorogood, Br J Obstet Gyn. 1998; Hernán, Neurol 2000)
 - ◆ Increased risk in long-term users (Hernán, Neurol 2000)



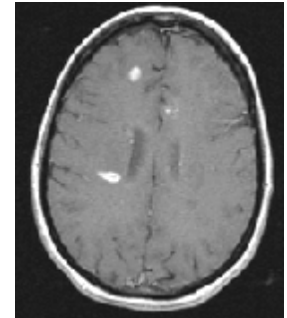
Confavreux, NEJM 1998

Multiple Sclerosis Sex Differences

MRI Measures

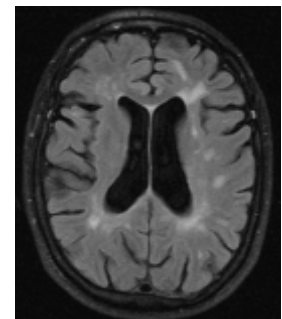
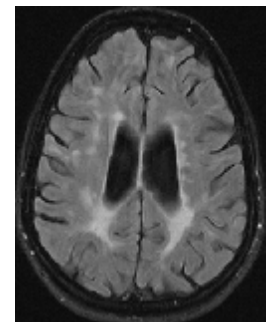
Active inflammation:

- ◆ Early and smaller studies (n = 50-413) found gadolinium-enhancing lesions more commonly in women. (Weatherby, J Neurol 2000; Pozzilli, EJM 2003; Tomassini, JNNP 2005)
- ◆ Later, larger studies (n = 763-1328) found no sex difference in gadolinium-enhancing lesions (Barkhof, Neurol 2005; Antulov, Mult Scler 2009)



Accumulated Injury:

- ◆ T2 lesions: no sex difference, after covariate adjustment (Tedeschi, Neurol 2005; Li, Neurol 2006, Antulov, Mult Scler 2009)
- ◆ T1 lesions: no sex difference in RRMS, SPMS; greater T1 lesion volume in male PPMS (Pozzilli, EJM 2003; Van Walderveen, Arch Neurol 2001; Antulov, Mult Scler 2009)
- ◆ Atrophy: no sex difference in cross-sectional studies or longitudinal studies (Kalkers, Arch Neurol 2002; Tedeschi, Neurol 2005; Giorgio, Neuroimaging Clinics N Am 2008; Antulov, Mult Scler 2009)
- ◆ Conflicting results with gray matter atrophy: greater in men (Antulov, Mult Scler 2009) or equal in men and women (Giorgio, Neuroimaging Clin N Am 2008)
- ◆ MTR, diffusion-weighted imaging: no sex difference (Antulov, Mult Scler 2009)



“It appears appropriate to conclude that gender does not seem to exert independent effects on morphologic changes of the brain as detected by MRI.” (Fazekas, JNS 2009)

Multiple Sclerosis Sex Differences Clinical Trials

Vast majority of clinical trials have found no effect of sex on outcome

- ◆ Many trials had pre-planned covariate analysis for sex
 - Most were silent on effect of sex (Sibley, *Neurol*, 1993; Arnason, *Neurol* 1999; Comi, *Ann Neurol* 2001; Clanet, *Neurol* 2002; Filippi, *Lancet* 2006)
 - Some reported no effect (Beck, *Ann Neurol* 2002; Kappos, *Neurol* 2006; Rudick, *NEJM* 2006)

Notable exceptions:

- ◆ Interferon (Rebif) secondary progressive MS trial: only women had slowed progression of disability (SPECTRIMS Study Group, *Neurol* 2001)
- ◆ Interferon (Betaseron) secondary progressive MS trial: only women had slowed progression of disability (Kappos, *Neurol* 2001)
 - Unclear if either study adjusted for other covariates
 - A 3rd interferon (Betaseron) secondary progressive MS trial found no effect of sex (NA Study Group on IFN β -1b in SPMS, *Neurol* 2004)
- ◆ Glatiramer acetate primary progressive MS trial: post-hoc analysis showed only men had slowed progression of disability (Wolinsky, *Ann Neurol* 2007)
 - Difference persisted after covariate adjustment (i.e. age, baseline disability, disease duration)
- ◆ Other interferon and glatiramer acetate trials showed no effect of sex (Rudick, *Arch Neurol* in press)

No relapsing remitting MS trial has shown a differential effect of sex on relapses

No clinical trial has shown a differential effect of sex on any MRI outcomes

(Wolinsky, *JNS* 2009)

Summary

Sex Differences in Multiple Sclerosis

- ◆ MS is 2-3x more common in women
 - Onset is later in men, and more likely to be PPMS
- ◆ Women may have a better prognosis
 - Differences decrease after adjusting for age at diagnosis and disease course (PPMS).
- ◆ Pregnancy decreases disease activity
 - Unclear effect of oral contraceptives
- ◆ In contrast to observations in smaller studies, large MRI studies suggest no effect of sex on MRI measures of either inflammation or tissue injury
- ◆ Pathology shows virtually no effect of sex
- ◆ Most clinical trials showed no effect of sex
 - A few post-hoc analyses found sex to be a significant covariate, but in different directions and not consistently between trials

Altogether, with the exception of incidence, there is little clinical evidence to suggest a sex difference in multiple sclerosis.