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REVIEW

Sexual disparities in the incidence and course of MS

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Abstract Multiple sclerosis (MS) affects three times more women than men and this ratio appears to be increasing. However male patients experience increased disease progression, brain atrophy, and cognitive impairment. Gonadal hormones may modulate these sex differences. For example, female puberty heralds an increased risk of MS, and during pregnancy disease activity is milder, with an increased risk of postpartum relapses. Gonadal hormones likely have complex and inflammatory and neuroprotective effects, and may interact with other disease modulators, such as vitamin D. Sex differences in the heritability of disease susceptibility genes implicate a role for epigenetic modification. Many questions remain, including the impact of sex on treatment response and epigenetic changes, and the modulatory potential of hormonal treatments. This article summarizes what is known about sexual dimorphism in MS onset and course, as well as potential interactions between sex and other factors influencing MS pathogenesis, incidence and severity.

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1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system. It affects three times more women than men, and onset occurs later in men than in women. However, men experience a more rapidly progressive clinical and radiologic course. Because the peak age of MS incidence is during women's childbearing years (age 25–40), it is likely that reproductive hormones play a modulatory role. However, the ways in which, and to what degree, sex hormones affect disease incidence and severity remain unclear and are the topics of ongoing research. Furthermore, sex and sex hormones are likely implicated in complex interactions with environmental (sunlight, vitamin D), genetic and epigenetic (transmission of MHC risk alleles), and cultural (urbanization, female education) factors to influence MS risk and progression. This article will summarize what is known about sexual dimorphism in MS onset and course, as well as in potential interactions between sex, sex hormones and other risk factors to influence MS pathogenesis, incidence and severity.

2. Sexual dimorphism in MS incidence and severity

2.1. Sex differences in incidence/prevalence

Starting with Jean-Martin Charcot's description of MS and at many points prior to the 1940s, it was believed that there was an excess of male cases. This was likely due to ascertainment bias, with dominance of men in the workforce and mischaracterization of women as hysterical. Since the National Multiple Sclerosis Society (NMSS) reported in the 1940s that the sex ratio was 1:1 [1], an increasing F:M sex ratio has emerged and continues to grow, reaching 2:1 in the 1980s [2] and approaching and even exceeding 3:1 today

[3–7]. The Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS) study, with unique epidemiological strengths, was particularly influential in this endeavor. It applied a sex ratio analysis within the cohort of over 30,000 Canadian families with at least one family member with MS to show an increasing F:M ratio in Canada over 50 years and now exceeding 3.2:1. This increasing trend has been noted not only in Western societies, but also in Iran, among others [8].

2.2. Sex differences in MS risk from CIS events

Generally, it is thought that female sex is associated with higher risk of developing clinically definite MS (CDMS) after a first demyelinating event [9]. In optic neuritis (ON), the best studied presentation of CIS, earlier studies suggesting an increased risk in females [10] were substantiated in patients with acute ON and no baseline MRI findings in the Optic Neuritis Treatment Trial (ONTT) after 15 years of follow up [11]. Further investigations found that both gender and MRI features were independent risk factors for the development of CDMS after ON [12]. These findings have been replicated in non-Western societies as well [13–15]. Additionally, not only female sex but specific exposures to gonadal hormones, such as subsequent pregnancy, may increase the risk of CDMS after CIS [16].

3. Sex differences in MS disease course and severity

3.1. Clinical course

Although men have a lower risk of developing MS than women, on aggregate natural history studies have suggested that male sex is a risk factor for a progressive onset of the disease (reviewed in [17]), poor recovery after initial attacks [18], more rapid accrual of disability and progression of EDSS

[17,19], and an overall more malignant course [20]. Conversely, females are more likely to manifest benign MS [17]. Sex does not appear to influence relapse rate [17]. These sex differences are likely not attributable only to sex influences on age and disease type at onset. For example, in a study comparing disease progression in patients with adult onset (ages 18–49) versus late onset (50 years or older) MS, sex differences in disease progression were found only in RRMS subjects with adult onset: in this group, men reached an EDSS of 6 sooner than women when controlling for age and disease duration. This suggests that female sex before the age of 50 may be protective against disease progression in RRMS. In fact, the F:M ratio in primary progressive disease was 1:06:1, suggesting that most sex differences are found in younger individuals with RRMS [21].

3.2. Cognitive function and radiologic findings

Cognitive impairment (CI) occurs in 40–70% of all patients with MS, regardless of disease subtype [22], involving variably deficits in attention, information processing speed, memory, executive function, and visual spatial perception. The prevalence of CI in MS increases from 30% to 40–48% patients at 2 years and 53% at 5 years, and may progress independently of disease severity [23–25]. Men with MS have been reported to experience more cognitive impairment (CI) [26–28]. Additionally, CI is associated with such risk factors as disease duration, disease severity (EDSS), and the APO-E4 risk allele for dementia in male but perhaps not female subjects [29].

There is a paucity of investigations of sex differences in neuroimaging features in MS. Some early studies suggested a higher T1/T2 ratio in men than in women (i.e. fewer T2 lesions but more evolved into “black holes”), and fewer enhancing lesions, raising the possibility of fewer inflammatory but more destructive lesions in men, and sex differences in susceptibility to demyelination and repair [30]. A subsequent review concluded that there was not likely a strong effect of sex on imaging features; notably, in controlling for disability as well as age and disease duration, the effect of sex on both disability and imaging features might be lost [31]. More recently, an appreciation of increased gray matter atrophy in males has emerged [32], particularly of the thalamus, which is highly correlated with cognitive impairment in adults [33] and children [34] with MS. In addition to education and thalamic volume, sex best predicts average cognition in MS patients [35]. Studies of functional connectivity have revealed decreased functional connectivity and network efficiency in men with MS, correlated with reduced visuospatial memory, relative to women with MS or male healthy controls, after adjusting for age, disease duration and disability [36].

3.3. Effects of disease modifying treatments (DMTs)

Very little is known about the potential effect of sex on response to DMTs.

3.3.1. Interferons

In a study of 2750 IFN beta-treated RRMS patients in 15 Italian centers (with 41% treated for up to 2 years, 39% for 2–4 years and 20% for >4 years), men had a significantly lower risk for 1st relapse ($p = 0.0097$) and a trend ($p = 0.0897$) for a

higher risk to reach 1 point EDSS progression than women [37]. However, there were no sex differences in a Cleveland Clinic study of IFN β -1a [38]. In SPMS, there is some suggestion that IFN β -1a may preferentially benefit women [39].

3.3.2. Glatiramer acetate (GA)

An initial post-hoc analysis of the PROMISE trial suggested an effect of GA on PPMS in men only but not women. However, subsequent analyses found no effect of sex on response to GA in either PPMS or RRMS [40,41].

3.3.3. Natalizumab

In subgroup analyses of the AFFIRM (natalizumab vs. placebo) and SENTINEL (natalizumab vs. placebo, all patients also received interferon beta-1a) trials, there was an effect of natalizumab on relapse rate in both men and women, but an effect on disability progression was only in women [42]; the authors did not control for disease duration or baseline EDSS when performing analyses based on sex.

4. Sex differences by age of onset

Overall, peak age of MS onset is only slightly higher in men (25 years) and than in women (24 years) [43], with some suggestion that age at presentation is increasing over time.

4.1. Pediatric onset (first symptoms before age 18)

Generally, POMS encompasses between 2–5% of all MS cases and is associated with a more inflammatory and relapsing course, with short interval between relapses, hyperacute presentation, and presence of encephalopathy [44–47].

As outlined below in greater detail, sex ratios that are approximately balanced prior to puberty, increase to 3:1 with onset of MS around the age of 12, or puberty [45,46].

Sex does not appear to play a major role in disease course in children [47–50]. Additionally, few studies have examined the impact of sex on developing a second relapse after CIS; some have found the risk after ON [51] or an acute demyelinating syndrome [52] in females to be elevated, but others have found no impact of sex on early second relapse after CIS [53,54].

In acute disseminated encephalomyelitis (ADEM), an entity mainly affecting children and adolescents and which may or may not represent a variant of or precursor for MS [55], there is in the balance, a slight preponderance of males [56].

4.2. Late onset (first symptoms after age 50)

Generally, onset of MS after age 50 (LOMS) encompasses between 3–12% of all MS cases and is associated with more frequent progressive course at onset [57,58], a more rapidly progressive course [21,59,60], and fewer inflammatory episodes and new gadolinium enhancing lesions [58,61] than in adult onset MS (AOMS).

The high F:M ratio in AOMS attenuates in LOMS (reported between 1.4:1 and 1:86:1) [21,58,59,62], although there is variability in age ranges used in these studies to characterize “adult”, or “young” onset MS. With respect to symptoms, in LOMS where patients are more likely to present with motor

and coordination complaints [58,59,62–64], men in particular are more likely to present with motor symptoms than women. Additionally, compared with AOMS, LOMS women but not men present with more coordination problems [21].

Although, male sex exerts an independent effect on the risk of a progressive disease onset, when patients are stratified by disease type, LOMS men and women progressed similarly, whereas AOMS men progressed more rapidly than women [21]. This finding suggests that endocrine, neurobiological or immunologic changes, potentially related to menopause, may cause older women to behave more similarly to men.

5. Potential mechanisms underlying sexual dimorphism in MS

5.1. Immunologic abnormalities in MS

Studies of immune responses in adult-onset MS, as well as lessons from therapeutic trials targeting various aspects of immune response, and data generated from animal models have led to a simplified model of MS immune-pathophysiology. The initial step is believed to be the peripheral activation of CD4⁺ T cells in response to a stimulating antigen, during which the profile of molecules including costimulatory signals and cytokines, influences the response profile of the activated immune cells [65]. The initial stimulating antigen is unknown, but has been postulated to be an infectious antigen, which subsequently causes cross-reactivity with a CNS antigen, termed “molecular mimicry”. Subsequently, transmigration of the activated T cells across the blood brain barrier (BBB), involving steps of adhesion, chemoattraction and active infiltration into the CNS leads to reactivation of infiltrating cells within the CNS, contributing to peri-vascular inflammation and injury. Release of additional CNS antigens may result in the recruitment of T cells with specificities for additional CNS antigens, termed ‘epitope spreading’, which may also serve to propagate a chronic immune response.

5.2. Effects of sex hormones on immunologic abnormalities in MS

Sex hormones, including estrogen and testosterone, but also progesterone and prolactin, have numerous well-studied effects upon immune function. In addition to these effects, these hormones may also protect against neurodegeneration, and thus play variable roles overall on the course of disease. These are summarized here and detailed in Chapter 4.

5.2.1. Estrogen

Animal data from experimental autoimmune encephalitis (EAE), the animal model of MS, support the idea of a biphasic dose effect of estrogen on inflammation. At lower levels, estrogens may promote inflammation; however, at high levels such as during pregnancy, estradiol may shift the immune response from a T helper 1 to T helper 2 imbalance, down-regulating proinflammatory cytokines (TNF- α and IFN- γ) and upregulating suppressor cytokines (IL-10), and muting inflammation. In addition to its role in inflammation, studies of ovariectomized animals suggest that estrogen may

also be neuroprotective (reviewed in [66–68]); this may have implications for the post-menopausal trajectory. In a pilot clinical trial involving 10 patients with MS, pregnancy-dose estradiol was found to have beneficial effects in reducing the number of gadolinium-enhancing lesions, in RRMS subjects but not in progressive subjects [69].

5.2.2. Testosterone

In contrast to the primarily “female” gonadal hormones, the potential anti-inflammatory and neuroprotective properties of testosterone remain underexplored for both men and women in MS [68,70]. In animal models of EAE, androgen deficiency following castration in males has resulted in a more inflammatory milieu and increased disease activity [71–74]. Treatment of castrated animals with testosterone, particularly DHT (which cannot be aromatized to estrogens, thus demonstrating androgen-specific effects) has resulted in alleviation of symptoms and inflammation [72,75–77]. In men with MS, relative androgen deficiency has been noted in some studies [78–81] but these studies had important limitations (reviewed in Chapter 12). In women with MS, testosterone levels may correlate negatively with disability and radiologic markers [80]. Epidemiologically, it could be hypothesized that the later age of onset of MS in men relative to women, may result from the age-related decline in protective testosterone levels [82]. In a pilot clinical trial of 10 men with MS (age < 65 years), treatment with testosterone gel for 12 months was associated with significant improvement in cognitive performance, slowing of the rate of brain atrophy [83], and altered immunologic profiles [84].

6. Effect of female reproductive exposures on disease course

6.1. Puberty

With the onset of puberty, the F:M incidence ratios rise from 1:1 to 3:1 [44–46,85]. Early puberty in girls, but not in boys, is associated with increased risk of MS [86]. In women with PPMS, early puberty is also associated with more rapid progression to EDSS 6 [87]. Thus the onset of menarche and exposure to reproductive hormones appears to herald in an increased risk of MS in females (see Chapter 7).

6.2. Pregnancy

6.2.1. Course during pregnancy

Pregnancy particularly the third trimester is a time of relative quiescence for MS, with a rebound in relapses noted in the first trimester postpartum [88,89]. The potential for hormonal modulation of relapse risk has been investigated [90] but has not thus far been demonstrated to be effective.

6.2.2. Breastfeeding

Breastfeeding, especially exclusive, may be protective against postpartum relapses [91,92]. The introduction of supplementary feeding in exclusively breastfed infants may provide an important hormonal cue for mothers, heralding in the increased risk of relapse postpartum. This is reviewed in more detail in Chapter 8.

6.2.3. Delayed childbearing

Delayed childbearing may be associated with increased risk of MS [93,94].

6.2.4. Parity

Overall, pregnancies may not negatively impact disease course [88,95,96]. In fact, a higher cumulative number of pregnancies may be associated with delay in reaching EDSS 6 in RRMS women [87], and having 3 or more children was felt to be protective in earlier studies [97].

6.2.5. Caution

The assessment of the impact of pregnancy and breast-feeding on disease course may be confounded by maternal age [96], and impacted by differential reproductive and therapeutic choices in women with MS based on their diagnosis of MS, and by their assessment of disease severity, personal well-being, and concerns about potential impact of disease or treatments on their fetus [98–100].

6.3. Oral contraceptive use

Women with MS may have higher rates of OCP use than controls [94]. In observational studies, no effect of OCP use

was observed on MS course [101,102]. Interestingly, in women with PPMS, OCP use has been associated with increased risk of progression to EDSS 6 [87]. In one small study of 10 women with MS, estriol, the estrogen most elevated during pregnancy, given at pregnancy doses was found to reduce the number of gadolinium-enhancing lesions on MRI in women with relapsing remitting MS only [69].

6.4. Menopause

There are no objective published data on the impact of the menopausal transition, or of the use of hormone replacement therapies, on the course of MS (See Chapter 12).

7. Genetic, behavioral and environmental interactions with sex

The observation of a rapidly increasing proportional difference between sexes in susceptibility to RRMS, has led to an investigation of the interactions between female sex and reproductive hormones, and environmental (e.g. sunlight exposure), behavioral (e.g. smoking, female education),

Table 1 Selected genetic, environmental and lifestyle factors with potentially sexually dimorphic effects on MS disease susceptibility and progression.

Smoking	- Smoking may increase the risk of MS in women only [124,125]. - Potential mechanisms may include an interaction between sex and smoking to yield increased levels of mature peripheral functioning T cells (OKT3⁺) in female smokers [126]. - The increasing F:M ratio in MS parallels that in smoking; but in smoking a higher F:M ratio may be driven both by decreasing rates in males [127] as well as by increased smoking rates in females [94].
Vitamin D	A functional synergy between 1,25(OH) D(3) and 17-β estradiol has been observed, mediated through estrogen receptor α, mainly in women and secondarily in men [103–105]: as a consequence, vitamin D seems to play an immunomodulatory role in MS mainly in women [128].
Uric acid	Urate, an antioxidant, is significantly lower in females than males in all types of MS [129].
Sunlight	Sunlight deprivation has worse consequences in women than in men [130].
Westernizing gender norms	- In some areas where the F:M ratio in MS is increasing, girls have experienced rapid increases in time spent indoors as a result of rapid urbanization, education and participation in the workforce [8,94]. - There has been a dramatic shift in women's reproductive choices and trajectories in the past century (see text).
Diet and metabolism	- Overweight/obesity at ages 18–20 may double the risk of MS [131,132], but not overweight/obesity in childhood (ages 5 or 10) or adulthood [131]. - Only in female adults, obesity at MS onset may be associated with a twofold increased OR of a relapsing course at onset [133]. It is not known whether the association between overweight/obesity and MS is mediated by lower levels of vitamin D in overweight patients [134]. - Estrone produced by adipocytes may represent an important source of inflammatory signaling in both men and women.
EBV exposure	Anti-Epstein–Barr VCA immune globulin G levels may be positively correlated with female sex and HLA DR2 [135].
Genetics/epigenetics	- Genome-Wide Association Studies have historically controlled for sex, potentially ignoring an effect, if present, of SNPs on MS risk in one sex only. - There may be a maternal parent of origin effect in transmission of the risk of MS, and of the HLA-DRB1*1501 risk allele, even when the mother is not affected ([136], reviewed in [6]). - The HLA-DRB5*0101–HLA-DRB1*1501–HLA-DQA1*0102–HLA-DQB1*0602 extended haplotype is more common in female than in male patients [137], has a higher F:M ratio in MS subjects than in controls [138], and in families with 2 generations of MS, females in the latest generation have an increased frequency of HLA-DRB1*15 [139]. These findings suggest a sex-specific interaction between genes and environment leading to epigenetic regulation [6].

genetic and epigenetic (e.g. MHC Class II haplotypes) risk factors. These are summarized in Table 1, and are further reviewed in Chapters 3 and 5. Further studies should continue to investigate interactive effects; for example, since estradiol and vitamin D levels are noted to interact [103–105], as are vitamin D receptor polymorphisms and HLA susceptibility alleles [106], could this locus of interactions explain some sexual dimorphism in MS risk? It should be noted that gender bias in recall of exposures may play an important role in some studies reporting sex differences in environmental risk factors [107,108], with men underreporting exposures relative to women.

8. Sex differences in non-demyelinating aspects of MS

In addition to sex differences in demyelination and disease progression, there may also be sex differences in the co-morbidities, disease sequelae and mortality associated with MS.

For example, in one survey of 4700 patients with MS who were commercially insured and taking a DMT, in adjusted analyses women reported better awareness of disease symptoms, of exacerbation management and of treatment options, suggesting that men may require additional education and support in managing their disease and treatments [109]. In terms of quality of life, men experience more CI than women (see above), reduced quality of life with respect to mental well being, and greater impact of perceived disability on quality of life [110]. Conversely, women may experience reduced quality of life in physical functioning dimensions [111] (although contradicted by [112]), including more persistent fatigue [113], pain, discomfort, [114,115], and sexual dysfunction [116], with decreased attention paid to their needs [115]. Little is known about sex differences in terms of co-morbidities and osteopenia, two common features of MS [117,118]. Finally, in terms of life expectancy, female patients likely have a longer median time to death and higher survival rates than male patients [17,119–121] although this is not borne out in all studies [122,123]. Nonetheless, women with MS may experience a higher relative risk of dying compared to women in the general population [119]. More research is needed to clarify sex-specific unmet needs in these areas.

9. Conclusions

Sex differences in MS incidence and severity result from a complex interaction of hormonal, genetic, and epigenetic factors. MS affects three times more women than men; yet in men disease onset is later and course is more rapidly progressive. The potential role for epigenetic modifications in the pathogenesis and progression of MS may further clarify how genetic, hormonal and environmental risk factors interact in the development of MS in men and in women.

Conflict of interest

The authors declare that there are no conflicts of interest.

References

- [1] O.E. Buckley, The status of multiple sclerosis, *Ann. N. Y. Acad. Sci.* 58 (1954) 541–720.
- [2] C. Confavreux, G. Aimard, M. Devic, Course and prognosis of multiple sclerosis assessed by the computerized data processing of 349 patients, *Brain* 103 (1980) 281–300.
- [3] N. Grytten, S.B. Glad, J.H. Aarseth, H. Nyland, R. Midgard, K.M. Myhr, A 50-year follow-up of the incidence of multiple sclerosis in Hordaland County, Norway, *Neurology* 66 (2006) 182–186.
- [4] A. Alonso, M.A. Hernan, Temporal trends in the incidence of multiple sclerosis: a systematic review, *Neurology* 71 (2008) 129–135.
- [5] A. Alonso, S.S. Jick, M.J. Olek, M.A. Hernan, Incidence of multiple sclerosis in the United Kingdom: findings from a population-based cohort, *J. Neurol.* 254 (2007) 1736–1741.
- [6] A.D. Sadovnick, European Charcot Foundation Lecture: the natural history of multiple sclerosis and gender, *J. Neurol. Sci.* 286 (2009) 1–5.
- [7] M.T. Wallin, W.J. Culpepper, P. Coffman, S. Pulaski, H. Maloni, C.M. Mahan, J.K. Haselkorn, J.F. Kurtzke, The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service, *Brain* 135 (2012) 1778–1785.
- [8] A.H. Maghzi, H. Ghazavi, M. Ahsan, M. Etemadifar, S. Mousavi, F. Khorvash, A. Minagar, Increasing female preponderance of multiple sclerosis in Isfahan, Iran: a population-based study, *Mult. Scler.* 16 (2010) 359–361.
- [9] Y. Liu, Y. Duan, C. Yu, W. Qin, H. Chen, H. Dong, J. Ye, H. Butzkueven, K. Li, Clinical isolated syndrome: a 3-year follow-up study in China, *Clin. Neurol. Neurosurg.* 113 (2011) 658–660.
- [10] E. Kinnunen, The incidence of optic neuritis and its prognosis for multiple sclerosis, *Acta Neurol. Scand.* 68 (1983) 371–377.
- [11] Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up, *Arch. Neurol.* 65 (2008) 727–732.
- [12] J.K. Swanton, K.T. Fernando, C.M. Dalton, K.A. Miszkiet, D.R. Altmann, G.T. Plant, A.J. Thompson, D.H. Miller, Early MRI in optic neuritis: the risk for clinically definite multiple sclerosis, *Mult. Scler.* 16 (2010) 156–165.
- [13] Y.C. Lin, M.Y. Yen, W.M. Hsu, H.C. Lee, A.G. Wang, Low conversion rate to multiple sclerosis in idiopathic optic neuritis patients in Taiwan, *Jpn. J. Ophthalmol.* 50 (2006) 170–175.
- [14] M. Mamarabadi, H. Razjouyan, F. Mohammadi, M. Moghaddasi, Assessment of outcome predictors after first attack of optic neuritis, *Can. J. Neurol. Sci.* 38 (2011) 887–895.
- [15] S.F. Kazim, M. Islam, M. Khan, B. Hameed, S. Shafqat, Risk of multiple sclerosis after idiopathic optic neuritis in a Pakistani population, *Can. J. Neurol. Sci.* 37 (2010) 258–263.
- [16] C. Lebrun, E. Le Page, O. Kantarci, A. Siva, D. Pelletier, D.T. Okuda, Impact of pregnancy on conversion to clinically isolated syndrome in a radiologically isolated syndrome cohort, *Mult. Scler.* 18 (2012) 1297–1302.
- [17] C. Confavreux, A. Compston, Chapter 4 – the natural history of multiple sclerosis, *McAlpine's Multiple Sclerosis, Fourth edition*, Churchill Livingstone, Edinburgh, 2006, pp. 183–272.
- [18] T.F. Scott, C.J. Schramke, Poor recovery after the first two attacks of multiple sclerosis is associated with poor outcome five years later, *J. Neurol. Sci.* 292 (2010) 52–56.
- [19] C. Confavreux, S. Vukusic, P. Adeleine, Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process, *Brain* 126 (2003) 770–782.
- [20] T. Gholipour, B. Healy, N.F. Baruch, H.L. Weiner, T. Chitnis, Demographic and clinical characteristics of malignant multiple sclerosis, *Neurology* 76 (2011) 1996–2001.
- [21] R.M. Bove, B. Healy, A. Augustine, A. Musallam, T. Gholipour, T. Chitnis, Effect of gender on late-onset multiple sclerosis, *Mult. Scler.* 18 (2012) 1472–1479.

- [22] C. Potagas, E. Giogkaraki, G. Koutsis, D. Mandellos, E. Tsirempoulou, C. Sfagos, D. Vassilopoulos, Cognitive impairment in different MS subtypes and clinically isolated syndromes, *J. Neurol. Sci.* 267 (2008) 100–106.
- [23] S. Simioni, C. Ruffieux, J. Kleeberg, L. Bruggimann, R.A. du Pasquier, J.M. Annoni, M. Schlupe, Progressive decline of decision-making performances during multiple sclerosis, *J. Int. Neuropsychol. Soc.* 15 (2009) 291–295.
- [24] B. Duque, J. Sepulcre, B. Bejarano, L. Samaranch, P. Pastor, P. Villoslada, Memory decline evolves independently of disease activity in MS, *Mult. Scler.* 14 (2008) 947–953.
- [25] M. Summers, L. Fisniku, V. Anderson, D. Miller, L. Cipolotti, M. Ron, Cognitive impairment in relapsing–remitting multiple sclerosis can be predicted by imaging performed several years earlier, *Mult. Scler.* 14 (2008) 197–204.
- [26] W.W. Beatty, D.E. Goodkin, D. Hertsgaard, N. Monson, Clinical and demographic predictors of cognitive performance in multiple sclerosis. Do diagnostic type, disease duration, and disability matter? *Arch. Neurol.* 47 (1990) 305–308.
- [27] W.W. Beatty, R.L. Aupperle, Sex differences in cognitive impairment in multiple sclerosis, *Clin. Neuropsychol.* 16 (2002) 472–480.
- [28] R.H. Benedict, R. Zivadinov, Risk factors for and management of cognitive dysfunction in multiple sclerosis, *Nat. Rev. Neurol.* 7 (2011) 332–342.
- [29] G. Savettieri, D. Messina, V. Andreoli, S. Bonavita, C. Caltagirone, R. Cittadella, D. Farina, M.C. Fazio, P. Girlanda, F. Le Pira, M. Liguori, A. Lugaresi, U. Nocentini, A. Reggio, G. Salemi, G. Tedeschi, M. Trojano, P. Valentino, A. Quattrone, Gender-related effect of clinical and genetic variables on the cognitive impairment in multiple sclerosis, *J. Neurol.* 251 (2004) 1208–1214.
- [30] C. Pozzilli, V. Tomassini, F. Marinelli, A. Paolillo, C. Gasperini, S. Bastianello, 'Gender gap' in multiple sclerosis: magnetic resonance imaging evidence, *Eur. J. Neurol.* 10 (2003) 95–97.
- [31] F. Fazekas, C. Enzinger, M. Wallner-Blazek, S. Ropele, A. Pluta-Fuerst, S. Fuchs, Gender differences in MRI studies on multiple sclerosis, *J. Neurol. Sci.* 286 (2009) 28–30.
- [32] R. Antulov, B. Weinstock-Guttman, J.L. Cox, S. Hussein, J. Durfee, C. Caiola, M.G. Dwyer, N. Bergsland, N. Abdelrahman, M. Stosic, D. Hojnacki, F.E. Munschauer, D. Miletic, R. Zivadinov, Gender-related differences in MS: a study of conventional and nonconventional MRI measures, *Mult. Scler.* 15 (2009) 345–354.
- [33] M.K. Houtchens, R.H. Benedict, R. Killiany, J. Sharma, Z. Jaisani, B. Singh, B. Weinstock-Guttman, C.R. Guttmann, R. Bakshi, Thalamic atrophy and cognition in multiple sclerosis, *Neurology* 69 (2007) 1213–1223.
- [34] C. Till, R. Ghassemi, B. Aubert-Broche, A. Kerbrat, D.L. Collins, S. Narayanan, D.L. Arnold, M. Desrocher, J.G. Sled, B.L. Banwell, MRI correlates of cognitive impairment in childhood-onset multiple sclerosis, *Neuropsychology* 25 (2011) 319–332.
- [35] M.M. Schoonheim, V. Popescu, F.C. Rueda Lopes, O.T. Wiebenga, H. Vrenken, L. Douw, C.H. Polman, J.J. Geurts, F. Barkhof, Subcortical atrophy and cognition: sex effects in multiple sclerosis, *Neurology* 79 (2012) 1754–1761.
- [36] M.M. Schoonheim, H.E. Hulst, D. Landi, O. Ciccarelli, S.D. Roosendaal, E.J. Sanz-Arigita, H. Vrenken, C.H. Polman, C.J. Stam, F. Barkhof, J.J. Geurts, Gender-related differences in functional connectivity in multiple sclerosis, *Mult. Scler.* 18 (2012) 164–173.
- [37] M. Trojano, P. Russo, A. Fuiani, D. Paolicelli, E. Di Monte, E. Granieri, G. Rosati, G. Savettieri, G. Comi, P. Livrea, The Italian Multiple Sclerosis Database Network (MSDN): the risk of worsening according to IFN β exposure in multiple sclerosis, *Mult. Scler.* 12 (2006) 578–585.
- [38] R.A. Rudick, L. Kappos, R. Kinkel, M. Clanet, J.T. Phillips, R.M. Herndon, A.W. Sandrock, F.E. Munschauer III, Gender effects on intramuscular interferon beta-1a in relapsing–remitting multiple sclerosis: analysis of 1406 patients, *Mult. Scler.* 17 (2011) 353–360.
- [39] Randomized controlled trial of interferon- beta-1a in secondary progressive MS: clinical results, *Neurology* 56 (2001) 1496–1504.
- [40] J.S. Wolinsky, P.A. Narayana, K.P. Johnson, United States open-label glatiramer acetate extension trial for relapsing multiple sclerosis: MRI and clinical correlates, Multiple Sclerosis Study Group and the MRI Analysis Center, *Mult. Scler.* 7 (2001) 33–41.
- [41] J.S. Wolinsky, T. Shochat, S. Weiss, D. Ladkani, Glatiramer acetate treatment in PPMS: why males appear to respond favorably, *J. Neurol. Sci.* 286 (2009) 92–98.
- [42] M. Hutchinson, L. Kappos, P.A. Calabresi, C. Confavreux, G. Giovannoni, S.L. Galetta, E. Havrdova, F.D. Lublin, D.H. Miller, P.W. O'Connor, J.T. Phillips, C.H. Polman, E.W. Radue, R.A. Rudick, W.H. Stuart, A. Wajgt, B. Weinstock-Guttman, D.R. Wynn, F. Lynn, M.A. Panzara, The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL, *J. Neurol.* 256 (2009) 405–415.
- [43] D.W. Paty, J.H. Noseworthy, G.C. Ebers, Diagnosis of multiple sclerosis, in: D.W. Paty, G.C. Ebers (Eds.), *Mult Scler*, FA Davis Company, Philadelphia, PA, 1997, pp. 48–51.
- [44] A. Ghezzi, Childhood–juvenile multiple sclerosis: clinical characteristics and treatment, *Expert Rev. Neurother.* 5 (2005) 403–411.
- [45] J.M. Ness, D. Chabas, A.D. Sadovnick, D. Pohl, B. Banwell, B. Weinstock-Guttman, Clinical features of children and adolescents with multiple sclerosis, *Neurology* 68 (2007) S37–S45.
- [46] T. Chitnis, B. Glanz, S. Jaffin, B. Healy, Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States, *Mult. Scler.* 15 (2009) 627–631.
- [47] M.P. Gorman, B.C. Healy, M. Polgar-Turcsanyi, T. Chitnis, Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis, *Arch. Neurol.* 66 (2009) 54–59.
- [48] A.J. Fay, E.M. Mowry, J. Strober, E. Waubant, Relapse severity and recovery in early pediatric multiple sclerosis, *Mult. Scler.* 18 (2012) 1008–1012.
- [49] R.F. Neuteboom, M. Boon, C.E. Catsman Berrevoets, J.S. Vles, R.H. Gooskens, H. Stroink, R.J. Vermeulen, J.J. Rotteveel, I.A. Ketelslegers, E. Peeters, B.T. Poll-The, J.F. De Rijk-Van Andel, A. Verrips, R.Q. Hintzen, Prognostic factors after a first attack of inflammatory CNS demyelination in children, *Neurology* 71 (2008) 967–973.
- [50] E.M. Mowry, M. Pesic, B. Grimes, S. Deen, P. Bacchetti, E. Waubant, Demyelinating events in early multiple sclerosis have inherent severity and recovery, *Neurology* 72 (2009) 602–608.
- [51] S. Sri-udomkajorn, K. Pongwatcharaporn, Clinical features and outcome of childhood optic neuritis at Queen Sirikit National Institute of Child Health, *J. Med. Assoc. Thai.* 94 (Suppl. 3) (2011) S189–S194.
- [52] B. Banwell, A. Bar-Or, D.L. Arnold, D. Sadovnick, S. Narayanan, M. McGowan, J. O'Mahony, S. Magalhaes, H. Hanwell, R. Vieth, R. Tellier, T. Vincent, G. Disanto, G. Ebers, K. Wambara, M.B. Connolly, J. Yager, J.K. Mah, F. Booth, G. Sebire, D. Callen, B. Meaney, M.E. Dilenge, A. Lortie, D. Pohl, A. Doja, S. Venketaswaran, S. Levin, E.A. Macdonald, D. Meek, E. Wood, N. Lowry, D. Buckley, C. Yim, M. Awuku, P. Cooper, F. Grand'maison, J.B. Baird, V. Bhan, R.A. Marrie, Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study, *Lancet Neurol.* 10 (2011) 436–445.

- [53] E.M. Mowry, M. Pesic, B. Grimes, S.R. Deen, P. Bacchetti, E. Waubant, Clinical predictors of early second event in patients with clinically isolated syndrome, *J. Neurol.* 256 (2009) 1061–1066.
- [54] E.M. Mowry, L.B. Krupp, M. Milazzo, D. Chabas, J.B. Strober, A.L. Belman, J.C. McDonald, J.R. Oksenberg, P. Bacchetti, E. Waubant, Vitamin D status is associated with relapse rate in pediatric-onset multiple sclerosis, *Ann. Neurol.* 67 (2010) 618–624.
- [55] L.B. Krupp, B. Banwell, S. Tenenbaum, Consensus definitions proposed for pediatric multiple sclerosis and related disorders, *Neurology* 68 (2007) S7–S12.
- [56] M. Tintore, G. Arrambide, Early onset multiple sclerosis: the role of gender, *J. Neurol. Sci.* 286 (2009) 31–34.
- [57] J.P. Hooge, W.K. Redekop, Multiple sclerosis with very late onset, *Neurology* 42 (1992) 1907–1910.
- [58] B. Kis, B. Rumberg, P. Berlit, Clinical characteristics of patients with late-onset multiple sclerosis, *J. Neurol.* 255 (2008) 697–702.
- [59] H. Tremlett, V. Devonshire, Is late-onset multiple sclerosis associated with a worse outcome? *Neurology* 67 (2006) 954–959.
- [60] J. Noseworthy, D. Paty, T. Wonnacott, T. Feasby, G. Ebers, Multiple sclerosis after age 50, *Neurology* 33 (1983) 1537–1544.
- [61] M. Filippi, J.S. Wolinsky, M.P. Sormani, G. Comi, Enhancement frequency decreases with increasing age in relapsing–remitting multiple sclerosis, *Neurology* 56 (2001) 422–423.
- [62] M.L. Polliack, Y. Barak, A. Achiron, Late-onset multiple sclerosis, *J. Am. Geriatr. Soc.* 49 (2001) 168–171.
- [63] S. Delalande, J. De Seze, D. Ferriby, T. Stojkovic, P. Vermersch, Late onset multiple sclerosis, *Rev. Neurol.* 158 (2002) 1082–1087.
- [64] B. Stankoff, S. Mrejen, A. Tourbah, B. Fontaine, O. Lyon-Caen, C. Lubetzki, M. Rosenheim, Age at onset determines the occurrence of the progressive phase of multiple sclerosis, *Neurology* 68 (2007) 779–781.
- [65] T. Chitnis, The role of CD4 T cells in the pathogenesis of multiple sclerosis, *Int. Rev. Neurobiol.* 79 (2007) 43–72.
- [66] M. El-Etr, S. Vukusic, L. Gignoux, F. Durand-Dubief, I. Achiti, E.E. Baulieu, C. Confavreux, Steroid hormones in multiple sclerosis, *J. Neurol. Sci.* 233 (2005) 49–54.
- [67] S.M. Gold, R.R. Voskuhl, Estrogen treatment in multiple sclerosis, *J. Neurol. Sci.* 286 (2009) 99–103.
- [68] S.M. Gold, R.R. Voskuhl, Estrogen and testosterone therapies in multiple sclerosis, *Prog. Brain Res.* 175 (2009) 239–251.
- [69] N.L. Sicotte, S.M. Liva, R. Klutch, P. Pfeiffer, S. Bouvier, S. Odesa, T.C. Wu, R.R. Voskuhl, Treatment of multiple sclerosis with the pregnancy hormone estriol, *Ann. Neurol.* 52 (2002) 421–428.
- [70] S.M. Liva, R.R. Voskuhl, Testosterone acts directly on CD4+ T lymphocytes to increase IL-10 production, *J. Immunol.* 167 (2001) 2060–2067.
- [71] K. Ganesan, C. Balachandran, B.M. Manohar, R. Puvanakrishnan, Comparative studies on the interplay of testosterone, estrogen and progesterone in collagen induced arthritis in rats, *Bone* 43 (2008) 758–765.
- [72] R. Panchanathan, H. Shen, M.G. Bupp, K.A. Gould, D. Choubey, Female and male sex hormones differentially regulate expression of Ifi202, an interferon-inducible lupus susceptibility gene within the Nba2 interval, *J. Immunol.* 183 (2009) 7031–7038.
- [73] B.F. Bebo Jr., E. Zelinka-Vincent, G. Adamus, D. Amundson, A.A. Vandenbark, H. Offner, Gonadal hormones influence the immune response to PLP 139–151 and the clinical course of relapsing experimental autoimmune encephalomyelitis, *J. Neuroimmunol.* 84 (1998) 122–130.
- [74] P.D. Fillmore, E.P. Blankenhorn, J.F. Zachary, C. Teuscher, Adult gonadal hormones selectively regulate sexually dimorphic quantitative traits observed in experimental allergic encephalomyelitis, *Am. J. Pathol.* 164 (2004) 167–175.
- [75] K. Ganesan, R. Selvam, R. Abhirami, K.V. Raju, B.M. Manohar, R. Puvanakrishnan, Gender differences and protective effects of testosterone in collagen induced arthritis in rats, *Rheumatol. Int.* 28 (2008) 345–353.
- [76] K.M. Palaszynski, K.K. Loo, J.F. Ashouri, H.B. Liu, R.R. Voskuhl, Androgens are protective in experimental autoimmune encephalomyelitis: implications for multiple sclerosis, *J. Neuroimmunol.* 146 (2004) 144–152.
- [77] D.R. Maccio, G. Calfa, G.A. Roth, Oral testosterone in male rats and the development of experimental autoimmune encephalomyelitis, *Neuroimmunomodulation* 12 (2005) 246–254.
- [78] T. Wei, S.L. Lightman, The neuroendocrine axis in patients with multiple sclerosis, *Brain* 120 (Pt 6) (1997) 1067–1076.
- [79] S.C. Foster, C. Daniels, D.N. Bourdette, B.F. Bebo Jr., Dysregulation of the hypothalamic–pituitary–gonadal axis in experimental autoimmune encephalomyelitis and multiple sclerosis, *J. Neuroimmunol.* 140 (2003) 78–87.
- [80] V. Tomassini, E. Onesti, C. Mainero, E. Giugni, A. Paolillo, M. Salvetti, F. Nicoletti, C. Pozzilli, Sex hormones modulate brain damage in multiple sclerosis: MRI evidence, *J. Neurol. Neurosurg. Psychiatry* 76 (2005) 272–275.
- [81] M.R. Safarinejad, Evaluation of endocrine profile, hypothalamic–pituitary–testis axis and semen quality in multiple sclerosis, *J. Neuroendocrinol.* 20 (2008) 1368–1375.
- [82] A. Pines, Male menopause: is it a real clinical syndrome? *Climacteric* 14 (2011) 15–17.
- [83] N.L. Sicotte, B.S. Giesser, V. Tandon, R. Klutch, B. Steiner, A.E. Drain, D.W. Shattuck, L. Hull, H.J. Wang, R.M. Elashoff, R.S. Swerdloff, R.R. Voskuhl, Testosterone treatment in multiple sclerosis: a pilot study, *Arch. Neurol.* 64 (2007) 683–688.
- [84] S.M. Gold, S. Chalifoux, B.S. Giesser, R.R. Voskuhl, Immune modulation and increased neurotrophic factor production in multiple sclerosis patients treated with testosterone, *J. Neuroinflammation* 5 (2008) 32.
- [85] M. Ruggieri, P. Iannetti, A. Polizzi, L. Pavone, L.M. Grimaldi, Multiple sclerosis in children under 10 years of age, *Neurol. Sci.* 25 (Suppl. 4) (2004) S326–S335.
- [86] S.V. Ramagopalan, W. Valdar, M. Crisculi, G.C. DeLuca, D.A. Dymant, S.M. Orton, I.M. Yee, G.C. Ebers, A.D. Sadovnick, Age of puberty and the risk of multiple sclerosis: a population based study, *Eur. J. Neurol.* 16 (2009) 342–347.
- [87] M.B. D'Hooghe, P. Haentjens, G. Nagels, T. D'Hooghe, J. De Keyser, Menarche, oral contraceptives, pregnancy and progression of disability in relapsing onset and progressive onset multiple sclerosis, *J. Neurol.* 259 (2012) 855–861.
- [88] C. Confavreux, M. Hutchinson, M.M. Hours, P. Cortinovis-Tournaire, T. Moreau, Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group, *N. Engl. J. Med.* 339 (1998) 285–291.
- [89] S. Vukusic, M. Hutchinson, M. Hours, T. Moreau, P. Cortinovis-Tournaire, P. Adeleine, C. Confavreux, G. The Pregnancy In Multiple Sclerosis, Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse, *Brain* 127 (2004) 1353–1360.
- [90] S. Vukusic, I. Ionescu, M. El-Etr, M. Schumacher, E.E. Baulieu, C. Cornu, C. Confavreux, The Prevention of Post-Partum Relapses with Progesterin and Estradiol in Multiple Sclerosis (POPARTMUS) trial: rationale, objectives and state of advancement, *J. Neurol. Sci.* 286 (2009) 114–118.
- [91] A. Langer-Gould, S.M. Huang, R. Gupta, A.D. Leimpeter, E. Greenwood, K.B. Albers, S.K. Van Den Eeden, L.M. Nelson, Exclusive breastfeeding and the risk of postpartum relapses in women with multiple sclerosis, *Arch. Neurol.* 66 (2009) 958–963.

- [92] K. Hellwig, A. Haghighia, M. Rockhoff, R. Gold, Multiple sclerosis and pregnancy: experience from a nationwide database in Germany, *Ther. Adv. Neurol. Disord.* 5 (2012) 247–253.
- [93] P. Holmqvist, M. Hammar, A.M. Landtblom, J. Brynhildsen, Age at onset of multiple sclerosis is correlated to use of combined oral contraceptives and childbirth before diagnosis, *Fertil. Steril.* 94 (2010) 2835–2837.
- [94] D. Kotzamani, T. Panou, V. Mastorodemos, M. Tzagournissakis, H. Nikolakaki, C. Spanaki, A. Plaitakis, Rising incidence of multiple sclerosis in females associated with urbanization, *Neurology* 78 (2012) 1728–1735.
- [95] N.M. Nielsen, K.T. Jorgensen, E. Stenager, A. Jensen, B.V. Pedersen, H. Hjalgrim, S.K. Kjaer, M. Frisch, Reproductive history and risk of multiple sclerosis, *Epidemiology* 22 (2011) 546–552.
- [96] S. Ramagopalan, I. Yee, J. Byrnes, C. Guimond, G. Ebers, D. Sadovnick, Term pregnancies and the clinical characteristics of multiple sclerosis: a population based study, *J. Neurol. Neurosurg. Psychiatry* 83 (2012) 793–795.
- [97] L. Villard-Mackintosh, M.P. Vessey, Oral contraceptives and reproductive factors in multiple sclerosis incidence, *Contraception* 47 (1993) 161–168.
- [98] S.C. Smeltzer, Reproductive decision making in women with multiple sclerosis, *J. Neurosci. Nurs.* 34 (2002) 145–157.
- [99] S. Alwan, I.M. Yee, M. Dybalski, C. Guimond, E. Dwosh, T.M. Greenwood, R. Butler, A.D. Sadovnick, Reproductive decision making after the diagnosis of multiple sclerosis (MS), *Mult. Scler.* 19 (2013) 351–358.
- [100] E. Portaccio, A. Ghezzi, B. Hakiki, V. Martinelli, L. Moiola, F. Patti, L. La Mantia, G.L. Mancardi, C. Solaro, M.R. Tola, C. Pozzilli, L. De Giglio, R. Totaro, A. Lugaresi, G. De Luca, D. Paolicelli, M.G. Marrosu, G. Comi, M. Trojano, M.P. Amato, Breastfeeding is not related to postpartum relapses in multiple sclerosis, *Neurology* 77 (2011) 145–150.
- [101] P. Holmqvist, M. Wallberg, M. Hammar, A.M. Landtblom, J. Brynhildsen, Symptoms of multiple sclerosis in women in relation to sex steroid exposure, *Maturitas* 54 (2006) 149–153.
- [102] S. Poser, N.E. Raun, J. Wikstrom, W. Poser, Pregnancy, oral contraceptives and multiple sclerosis, *Acta Neurol. Scand.* 59 (1979) 108–118.
- [103] G. Disanto, A.E. Handel, S.V. Ramagopalan, Estrogen–vitamin D interaction in multiple sclerosis, *Fertil. Steril.* 95 (2011) e3, (author reply e4).
- [104] J. Correale, M.C. Ysraelit, M.I. Gaitan, Gender differences in 1,25 dihydroxyvitamin D3 immunomodulatory effects in multiple sclerosis patients and healthy subjects, *J. Immunol.* 185 (2010) 4948–4958.
- [105] F.E. Nashold, K.M. Spach, J.A. Spanier, C.E. Hayes, Estrogen controls vitamin D3-mediated resistance to experimental autoimmune encephalomyelitis by controlling vitamin D3 metabolism and receptor expression, *J. Immunol.* 183 (2009) 3672–3681.
- [106] C. Agliardi, F.R. Guerini, M. Saresella, D. Caputo, M.A. Leone, M. Zanzottera, E. Bolognesi, I. Marventano, N. Barizzone, M.E. Fasano, N. Al-Daghri, M. Clerici, Vitamin D receptor (VDR) gene SNPs influence VDR expression and modulate protection from multiple sclerosis in HLA-DRB1*15-positive individuals, *Brain Behav. Immun.* 25 (2011) 1460–1467.
- [107] S.V. Ramagopalan, W. Valdar, D.A. Dymment, G.C. DeLuca, I.M. Yee, G. Giovannoni, G.C. Ebers, A.D. Sadovnick, Association of infectious mononucleosis with multiple sclerosis. A population-based study, *Neuroepidemiology* 32 (2009) 257–262.
- [108] S.V. Ramagopalan, D.A. Dymment, B.M. Herrera, M. Crisculoli, I.M. Yee, A.D. Sadovnick, G.C. Ebers, Clustering of autoimmune disease in families at high risk for multiple sclerosis? *Lancet Neurol.* 6 (2007) 206–207, (author reply 207).
- [109] A. Vlahiotis, R. Sedjo, E.R. Cox, T.E. Burroughs, A. Rauchway, R. Lich, Gender differences in self-reported symptom awareness and perceived ability to manage therapy with disease-modifying medication among commercially insured multiple sclerosis patients, *J. Manag. Care Pharm.* 16 (2010) 206–216.
- [110] I. Casetta, T. Riise, M. Wamme Nortvedt, N.T. Economou, R. De Gennaro, P. Fazio, E. Cesnik, V. Govoni, E. Granieri, Gender differences in health-related quality of life in multiple sclerosis, *Mult. Scler.* 15 (2009) 1339–1346.
- [111] O. Fernandez, K. Baumstarck-Barrau, M.C. Simeoni, P. Auquier, Patient characteristics and determinants of quality of life in an international population with multiple sclerosis: assessment using the MusiQoL and SF-36 questionnaires, *Mult. Scler.* 17 (2011) 1238–1249.
- [112] M. Pugliatti, T. Riise, M.W. Nortvedt, G. Carpentras, M.A. Sotgiu, S. Sotgiu, G. Rosati, Self-perceived physical functioning and health status among fully ambulatory multiple sclerosis patients, *J. Neurol.* 255 (2008) 157–162.
- [113] M. Mollaoglu, E. Ustun, Fatigue in multiple sclerosis patients, *J. Clin. Nurs.* 18 (2009) 1231–1238.
- [114] O. Hadjimichael, R.D. Kerns, M.A. Rizzo, G. Cutter, T. Vollmer, Persistent pain and uncomfortable sensations in persons with multiple sclerosis, *Pain* 127 (2007) 35–41.
- [115] R.J. Buchanan, S. Wang, H. Ju, Gender analyses of nursing home residents with multiple sclerosis, *J. Gend. Specif. Med.* 6 (2003) 35–46.
- [116] D.B. Celik, E.C. Poyraz, A. Bingol, E. Idiman, S. Ozakbas, D. Kaya, Sexual dysfunction in multiple sclerosis: gender differences, *J. Neurol. Sci.* 324 (2013) 17–20.
- [117] R.A. Marrie, R. Horwitz, G. Cutter, T. Tyry, Cumulative impact of comorbidity on quality of life in MS, *Acta Neurol. Scand.* 125 (2012) 180–186.
- [118] J. Nieves, F. Cosman, J. Herbert, V. Shen, R. Lindsay, High prevalence of vitamin D deficiency and reduced bone mass in multiple sclerosis, *Neurology* 44 (1994) 1687–1692.
- [119] N. Grytten Torkildsen, S.A. Lie, J.H. Aarseth, H. Nyland, K.M. Myhr, Survival and cause of death in multiple sclerosis: results from a 50-year follow-up in Western Norway, *Mult. Scler.* 14 (2008) 1191–1198.
- [120] D.S. Goodin, A.T. Reder, G.C. Ebers, G. Cutter, M. Kremenchutzky, J. Oger, D. Langdon, M. Rametta, K. Beckmann, T.M. DeSimone, V. Knappertz, Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNbeta-1b trial, *Neurology* 78 (2012) 1315–1322.
- [121] E. Leray, S.P. Morrissey, J. Yaouanq, M. Coustans, E. Le Page, J. Chaperon, G. Edan, Long-term survival of patients with multiple sclerosis in West France, *Mult. Scler.* 13 (2007) 865–874.
- [122] P. Ragonese, P. Aridon, M.A. Mazzola, G. Callari, B. Palmeri, G. Famoso, V. Terruso, G. Salemi, M. D'Amelio, G. Savettieri, Multiple sclerosis survival: a population-based study in Sicily, *Eur. J. Neurol.* 17 (2010) 391–397.
- [123] M.L. Sumelahti, P.J. Tienari, J. Wikstrom, T.M. Salminen, M. Hakama, Survival of multiple sclerosis in Finland between 1964 and 1993, *Mult. Scler.* 8 (2002) 350–355.
- [124] A. Alonso, S.D. Cook, A.H. Maghzi, A.A. Divani, A case–control study of risk factors for multiple sclerosis in Iran, *Mult. Scler.* 17 (2011) 550–555.
- [125] A. Rodriguez Regal, M. del Campo Amigo, J. Paz-Esquete, A. Martinez Feijoo, E. Cebrian, P. Suarez Gil, M.A. Mourino, A case–control study of the influence of the smoking behaviour in multiple sclerosis, *Neurologia* 24 (2009) 177–180.
- [126] R.C. Burton, P. Ferguson, M. Gray, J. Hall, M. Hayes, Y.C. Smart, Effects of age, gender, and cigarette smoking on human immunoregulatory T-cell subsets: establishment of normal ranges and comparison with patients with colorectal cancer and multiple sclerosis, *Diagn. Immunol.* 1 (1983) 216–223.

- [127] N. Palacios, A. Alonso, H. Bronnum-Hansen, A. Ascherio, Smoking and increased risk of multiple sclerosis: parallel trends in the sex ratio reinforce the evidence, *Ann. Epidemiol.* 21 (2011) 536–542.
- [128] J. Kragt, B. van Amerongen, J. Killestein, C. Dijkstra, B. Uitdehaag, C. Polman, P. Lips, Higher levels of 25-hydroxyvitamin D are associated with a lower incidence of multiple sclerosis only in women, *Mult. Scler.* 15 (2009) 9–15.
- [129] S. Zoccolella, C. Tortorella, P. Iaffaldano, V. Direnzo, M. D'Onghia, E. Luciannatelli, D. Paolicelli, P. Livrea, M. Trojano, Low serum urate levels are associated to female gender in multiple sclerosis patients, *PLoS One* 7 (2012) e40608.
- [130] K.M. Spach, C.E. Hayes, Vitamin D3 confers protection from autoimmune encephalomyelitis only in female mice, *J. Immunol.* 175 (2005) 4119–4126.
- [131] K.L. Munger, T. Chitnis, A. Ascherio, Body size and risk of MS in two cohorts of US women, *Neurology* 73 (2009) 1543–1550.
- [132] A.K. Hedstrom, T. Olsson, L. Alfredsson, High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women, *Mult. Scler.* 18 (2012) 1334–1336.
- [133] R.A. Marrie, R.I. Horwitz, G. Cutter, T. Tyry, T. Vollmer, Association between comorbidity and clinical characteristics of MS, *Acta Neurol. Scand.* 124 (2011) 135–141.
- [134] C.B. Turer, H. Lin, G. Flores, Prevalence of vitamin D deficiency among overweight and obese US children, *Pediatrics* 131 (2013) e152–e161.
- [135] T.R. Nielsen, M. Pedersen, K. Rostgaard, M. Frisch, H. Hjalgrim, Correlations between Epstein–Barr virus antibody levels and risk factors for multiple sclerosis in healthy individuals, *Mult. Scler.* 13 (2007) 420–423.
- [136] S.V. Ramagopalan, J.K. Byrnes, D.A. Dymment, C. Guimond, L. Handunnetthi, G. Disanto, I.M. Yee, G.C. Ebers, A.D. Sadovnick, Parent-of-origin of HLA-DRB1*1501 and age of onset of multiple sclerosis, *J. Hum. Genet.* 54 (2009) 547–549.
- [137] A.E. Hensiek, S.J. Sawcer, R. Feakes, J. Deans, A. Mander, E. Akesson, R. Roxburgh, F. Coraddu, S. Smith, D.A. Compston, HLA-DR 15 is associated with female sex and younger age at diagnosis in multiple sclerosis, *J. Neurol. Neurosurg. Psychiatry* 72 (2002) 184–187.
- [138] M.J. Chao, S.V. Ramagopalan, B.M. Herrera, S.M. Orton, L. Handunnetthi, M.R. Lincoln, D.A. Dymment, A.D. Sadovnick, G.C. Ebers, MHC transmission: insights into gender bias in MS susceptibility, *Neurology* 76 (2011) 242–246.
- [139] M.J. Chao, S.V. Ramagopalan, B.M. Herrera, M.R. Lincoln, D.A. Dymment, A.D. Sadovnick, G.C. Ebers, Epigenetics in multiple sclerosis susceptibility: difference in transgenerational risk localizes to the major histocompatibility complex, *Hum. Mol. Genet.* 18 (2009) 261–266.