MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Higher weight in adolescence and young adulthood is associated with an earlier age at multiple sclerosis onset

Multiple Sclerosis Journal

2015, Vol. 21(7) 858–865

DOI: 10.1177/1352458514555787

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Abstract

Background: Growing evidence suggests an association between adolescent obesity and increased risk of multiple sclerosis (MS).

Objective: The objective of this paper is to investigate whether weight or body mass index (BMI) in adolescence and young adulthood was associated with age at MS symptom onset.

Methods: Our cohort is comprised of a sub-group of 184 women enrolled in the New York State MS Consortium registry. Individuals were asked to recall their weight at the time of first menstruation and at age 25. BMI was calculated accordingly for age 25. Regression analyses were carried out to investigate the association between weight or BMI and age at onset.

Results: Weight at menarche was significantly related to younger age at symptom onset ($\beta = -0.073$, $p = 0.001$). These results were also found at age 25 for weight ($\beta = -0.080$, $p < 0.001$) and BMI ($\beta = -0.448$, $p = 0.001$). Significantly earlier disease onset (26.9 years ±9.9) was observed in individuals who were overweight at 25 compared to those who were not overweight (32.1 years ±9.2, $p = 0.006$).

Conclusions: Women who reported higher weight in adolescence and BMI in early adulthood were younger at MS onset. Future research should investigate whether there is a causal link between body weight and MS, as prevention lifestyle and dietary interventions could be implemented.

Keywords: Multiple sclerosis, obesity, weight, body mass index (BMI), age at onset, menarche

Date received: 26 June 2014; revised: 19 August 2014; 9 September 2014; accepted: 17 September 2014

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See acknowledgments for a list of participating investigators.

Introduction

Multiple sclerosis (MS) is a demyelinating neurodegenerative disease of the central nervous system and is the leading cause of non-traumatic neurological disability among young adults. Its incidence and prevalence vary greatly within different parts of the world, and a general increase of the occurrence of MS in women has been observed in the last few years.[1] The disease is more prevalent among females than males with a 2:1 female to male ratio, although in more recent years a 3:1 ratio was observed.[2]

The average age at symptoms onset is just below 30 years. Moreover, a recent study found a decreasing trend for age at MS onset.[3] Reasons for this decrease are currently unknown, but studies have linked an earlier age at onset in patients to being a carrier of the human leukocyte antigen (HLA)-DRB*15 allele[4] and overall MS genetic burden scores.[5] Recently, decreased sun exposure during childhood has also been linked to an earlier age at symptom onset.[6]

Recent studies have found an association between obesity in young adulthood and MS incidence. A prospective study carried out among school children in Denmark reported that high childhood and early adolescent body mass index (BMI) was found to be a strong risk factor for MS.[7] An earlier study by Munger et al. (2009) found a more than twofold increase in the risk of developing MS among women who were obese at age 18 compared to those who had a normal body weight, while no influence of overweight in early

childhood or in later adulthood was observed.[8] While this study was performed only in women, others found similar results both in males and females.[9,10] Yet others reported an association between childhood obesity and an increased risk of pediatric onset MS and clinically isolated syndrome (CIS), a result found in girls but not in boys.[11]

The exact mechanisms influencing the association of obesity with MS onset remain unclear. Studies have suggested a role of vitamin D,[12] leptin,[13] and earlier start of menses.[14,15] With the increasing rate of obesity in adolescence, it is of great importance to explore whether there are associations with chronic inflammatory degenerative diseases such as MS. In this study, we aimed to investigate whether self-reported higher weight or BMI in adolescence and young adulthood was associated with the age at MS onset in a sample of women with a clinical diagnosis of MS.

Methods

Study population

Participants are part of the New York State MS Consortium (NYSMSC). The NYSMSC was founded in 1996 and includes 12 centers throughout New York State and is one of the largest ongoing databases for MS patients, as described elsewhere.[16] Informed consent was obtained from all patients for inclusion in the study in compliance with institutional review board (IRB) policies for research with humans. This cohort study is part of an ongoing larger study evaluating reproductive events and its influence in women with MS. Data are based on information obtained from a survey distributed among women enrolled in the NYSMSC at the Buffalo, NY, site. The survey was distributed among 778 women. Out of the 268 people who responded, 237 participated and 31 declined to participate. Of the 237 participants, 53 were excluded for missing data on weight or age at symptom onset, leaving a total sample size of 184 individuals. The study period was between March 2012 and July 2013.

Weight and BMI measures

Women were asked to recall their weight at two time points: time of first menstruation (menarche) and at age 25 as well as their current height. BMI (kg/m^2) was calculated using self-reported weight at age 25 and current body height (weight (pounds (lb))/(height (in))^2 × 703), but was not extended to time of first menstruation, since height measures in adolescence could not reliably be deduced. BMI was used as a continuous measure as well as categorized into four groups: (1) underweight (BMI < 18.5), (2) normal weight (BMI 18.5–24.9), (3) overweight (BMI 25.0–29.9), and (4) obese (BMI ≥30) as determined using the World Health Organization's guidelines.[17] Based on this, two groups were compiled by combining the overweight individuals (groups 3 and 4), and the non-overweight individuals (groups 1 and 2). Additional analyses were carried out based on groups split by median age at symptom onset, and weight. Data on age at symptom onset and disability were available from the NYSMSC registry.

Statistical analyses

All data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows (version 21, SPSS Inc, Chicago, IL). Frequencies of underweight, normal weight, overweight, and obese weight were determined. Demographic characteristics were compared between those with early age at MS onset (groups divided on median) to those with a later MS onset, using independent samples *t*-tests and chi-square tests. Overweight and non-overweight individuals were also compared on demographic characteristics. Variables that were significantly different between the overweight/non-overweight groups were considered potential confounders in all subsequent analyses. Linear regression analyses were carried out to investigate the association between age at MS onset with weight (at menarche and age 25) and BMI (at age 25). In regression analyses (1) age at MS symptom onset was compared between weight groups (≤ median vs. > median) at both menarche and age 25, and (2) age at MS symptom onset between overweight/non-overweight status based on BMI classifications groups at age 25. Following these initial analyses, linear regression analyses were used to assess the association of (3) weight both at menarche and age 25 with age at MS symptom onset, and (4) BMI at age 25 with age at MS symptom onset. Additionally, to test for the effect of age at menarche, further interaction models were constructed. Finally, using analysis of covariance (ANCOVA), age at MS symptom onset was compared between specific groups based on BMI classifications (underweight, normal weight, overweight, obese). We considered a two-sided p value of <0.05 as statistically significant.

Results

Demographic and clinical characteristics

In analyses between participants with an age at MS onset ≤32 years vs. those who had a later onset, there were no significant differences regarding race,

Table 1. Clinical and demographical characteristics.

	Age MS onset <32	Age MS onset ≥32	*p* value
Race, *n* (%)			0.499
Caucasian	101 (98.1%)	76 (96.2%)	
African American	2 (1.9%)	2 (2.5%)	
Other	0	1 (1.3%)	
Education, *n* (%)			0.774
Less than college degree	22 (21.6%)	18 (23.4%)	
College degree or greater	80 (78.4%)	59 (76.6%)	
MS type, *n* (%)			0.005
RRMS	86 (83.5%)	65 (84.4%)	
SPMS	17 (16.5%)	5 (6.5%)	
PP/PRMS	0	4 (5.2%)	
Other	0	3 (3.9%)	
EDSS (SD)	2.7 (2.0)	2.4 (1.6)	0.258
Weight in pounds at time first menstruation (SD)	119.1 (35.7)	109.6 (23.6)	0.042
Weight in pounds at age 25 (SD)	141.4 (40.8)	126.6 (18.5)	0.001
BMI at age 25 (SD)	23.7 (6.3)	21.8 (3.1)	0.007

MS: multiple sclerosis; RR: relapsing–remitting; SP: secondary progressive; PP/PR: primary progressive/primary relapsing; EDSS: Expanded Disability Status Scale; BMI: body mass index (kg/m^2). *p* values were derived using chi-squared tests and independent samples *t*-tests. $p < 0.05$ was considered statistically significant.

education, and Expanded Disability Status Scale (EDSS) score (Table 1). Although there was a difference in MS type at study enrollment ($p = 0.005$), the ratio of relapsing vs. progressive MS types was similar between early and late MS onset groups. Furthermore, participants with an earlier MS onset were heavier both at menarche ($p = 0.042$) and age 25 ($p < 0.001$), and BMI at 25 was also higher in individuals with an earlier onset ($p = 0.007$). Additional group-wise analyses investigating differences between overweight and non-overweight participants at age 25 showed that there were no differences in education, EDSS or MS type between the overweight and the non-overweight group ($p > 0.05$), but African American patients were more likely to be overweight ($p < 0.001$). Significantly earlier disease onset (26.9 years ± 9.9) was observed in individuals who were overweight at 25 compared to those who were not overweight (32.1 years ± 9.2, $p = 0.006$). Race was used as a covariate in all subsequent regression models because of the observed group differences.

Associations of weight at menarche with age of MS onset

At first menstruation (mean 12.9 years ±2.1) the mean weight was 115.0 pounds (lbs.) (±31.3, median = 110). Two groups were created based on median weight at menarche (≤110 vs. >110 lbs.). Individuals in the ≤110 lbs. group were significantly older at disease onset (32.5±9.6) compared to the >110 lbs. group (29.5±9.1, $p = 0.023$; Figure 1(a)). Using weight as a continuous measure in linear regression analysis corroborated this finding: Weight was found to be inversely related to age at MS onset ($\beta = -0.073$, $p = 0.001$, Table 2). The significant results were limited to weight at menarche, as there was no significant association between age at menarche with age at MS onset ($p = 0.544$). Furthermore, an interaction term of weight and age at menarche was also found to not be significantly associated with age at MS onset ($p = 0.572$).

Associations of weight and BMI at age 25 with age of MS onset

At age 25, the mean weight was 135.0 lbs. (±33.7, median = 130), while mean BMI was 22.9 (±5.3). Regression analyses were carried out testing whether age at MS onset was different between groups split on weight (≤ 130 lbs. vs. > 130 lbs.) and overweight status based on BMI (≤ 25 vs. >25). An earlier age at MS onset was apparent in individuals classified in the high weight group ($p = 0.005$, Figure 1(b)), as well as being overweight ($p = 0.002$, Figure 1(c)). Table 2 gives an overview of the results of several linear regressions with weight, BMI, and age at MS onset as continuous variables. In line with the findings mentioned above, weight (at first menstruation and age

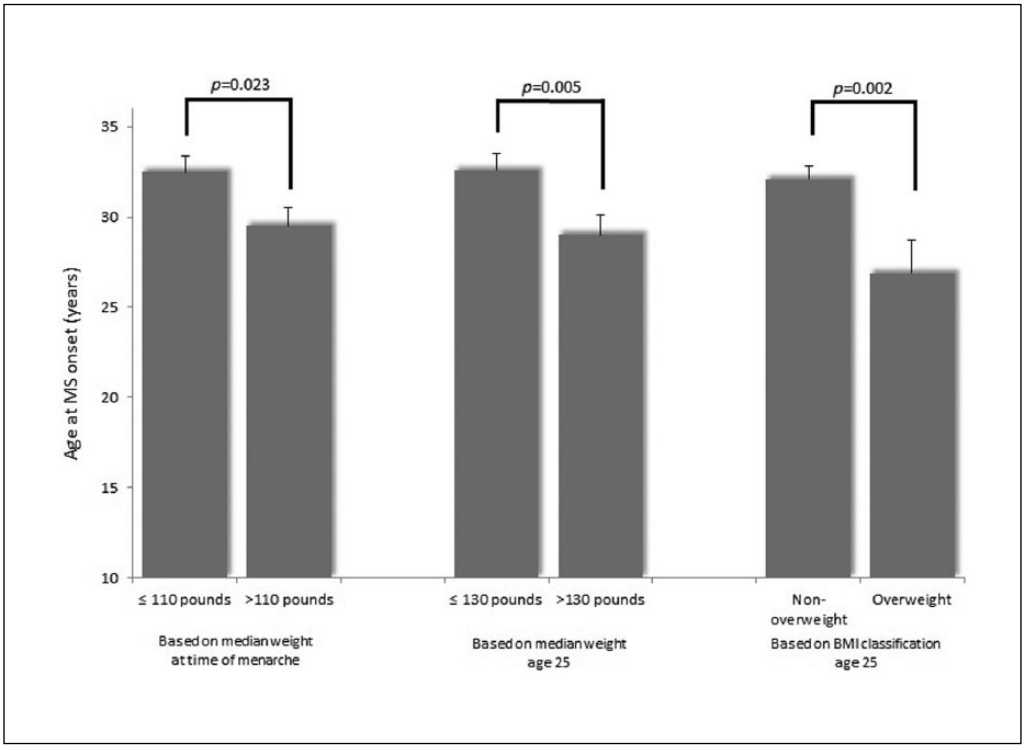

Figure 1. Age at MS onset of different weight groups.
Age at MS onset between patients who were (a) below (≤ 110 lbs.) or above (>110 lbs.) the median weight at menarche, (b) below (≤130 lbs.) or above (>130 lbs.) the median weight at age 25, and between (c) non-overweight (BMI ≤25) or overweight (BMI >25) at age 25 patients. MS: multiple sclerosis; lbs.: pounds; BMI: body mass index.

Table 2. Association of age at MS onset with weight at first menstruation and age 25 and BMI at age 25.

		Age MS symptom onset		
		β	95% CI	*p*
First menstruation	Weight	–0.073	(–0.116 to −0.031)	0.001
Age 25	Weight	–0.080	(–0.120 to −0.041)	<0.001
Age 25	BMI	–0.448	(–0.710 to −0.186)	0.001

MS: multiple sclerosis; BMI: body mass index; CI: confidence interval. *p* values were derived from (three separate) linear regression analyses. $p < 0.05$ was considered statistically significant.

25) and BMI (at age 25) were significantly related to age at MS onset.

Group-wise differences in age of MS onset using BMI classifications.

At age 25, 12 (6.5%) participants had a BMI classification as being underweight (BMI < 18.5), while 141 (76.6%) had a normal weight (BMI 18.5–25), 17 (9.2%) were overweight (BMI 25–30), and 14 (7.6%) were considered obese (BMI > 30). Women who were obese at age 25 had a significantly earlier age at MS onset compared to those who were underweight ($p = 0.009$) or normal weight ($p < 0.001$). Overweight individuals also tended to have an earlier age of MS onset, although this did not reach significance (Figure 2).

Discussion

To our knowledge, this is the first study investigating the relationship between weight in adolescence and early adulthood on the age of MS symptom onset. Our results show that a higher weight at menarche and at age 25 was significantly related to an earlier age at MS symptom onset. These results were extended to BMI: Higher BMI at age 25 was found to be associated with an earlier age at MS onset. Results were observed using several different statistical models.

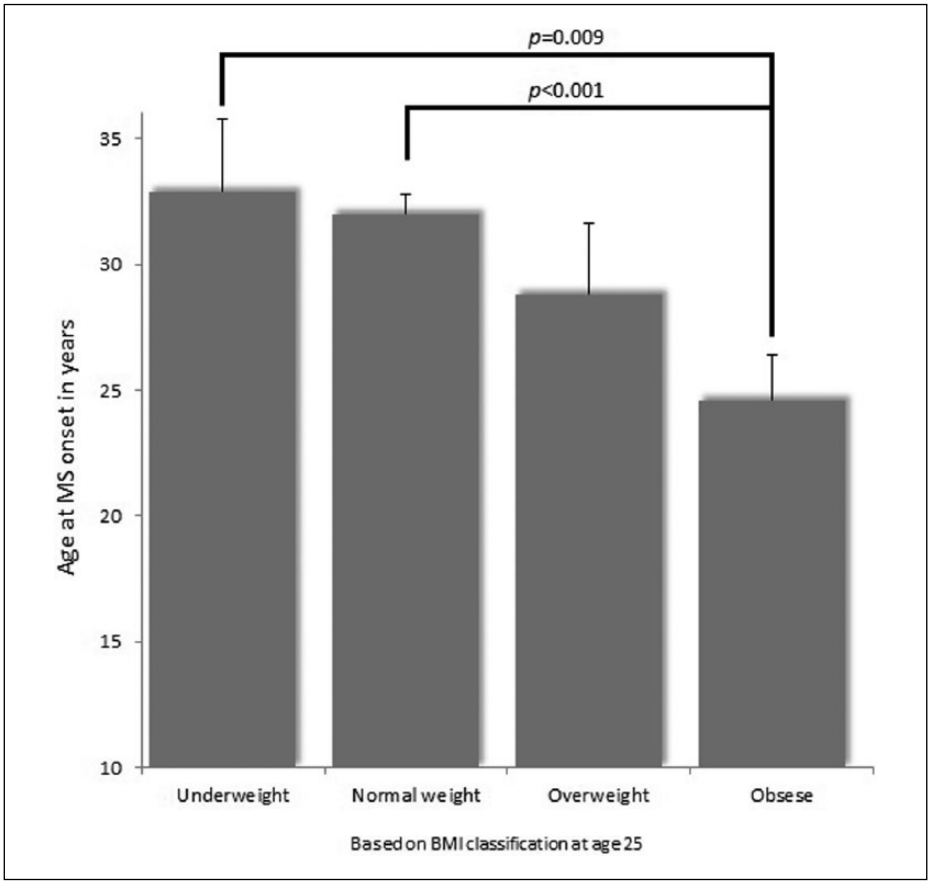

Figure 2. Age at MS symptom onset per BMI classification.
BMI <18.5, 18.5 to <25.0, 25.0 to <30.0, and ≥30.0 MS: multiple sclerosis; BMI: body mass index.

Based on our results, it appears that being overweight or obese early in life may be a risk factor not only for the development of MS,[7–11] but when it develops, that symptoms occur at an earlier age. It is unknown if being overweight or obese in early life has any influence on the actual course of MS disability, but our limited analyses indicate that there were no group differences at study enrollment in MS type or EDSS scores between those who were overweight and those who were not overweight at age 25.

The onset of puberty is strongly related to an increase in (sex) hormones. As hormones are known to affect MS,[18] several studies have been conducted to investigate how puberty onset is associated with MS. Researchers have found a relationship between weight and age at menarche; those with excess body weight tended to be younger at puberty onset.[19] A Canadian-based population cohort study reported an association between an earlier age at puberty onset and an increased risk of MS in women while results were not significant in men.[14] Another study linked an earlier age at menarche to a younger age at MS symptom onset,[15] while an older study failed to find such an association.[20] In our sample, we did not find an association between age at menarche and age at MS onset. Furthermore, there was no significant interaction effect of weight and age at menarche, indicating that the results found in our study appear to be driven by weight, not by age at menarche or the interaction thereof.

Prevalence of obesity has been on the rise in the past decades both in children[21] and adults,[22] and previous studies have linked obesity to MS by focusing on the risk of developing the disease.[7–11] A recent study investigated the interaction between obesity and the HLA-DRB1*15 allele known to be associated with an increased risk for developing MS, and found a 2.9-fold increase in risk comparing normal-weight (BMI 18.5–21) HLA-DRB1*15 carriers to normal-weight non-carriers. However, there was a 9.1-fold increase in risk when comparing obese (BMI ≥ 27) HLA-DRB1*15 carriers to normal-weight non-carriers.[10] This indicates that the influence of obesity on MS risk is also

dependent on genetic background. Although more evidence is warranted, weight could serve as a potential modifiable environmental risk factor with an ability to modulate the risk of developing MS among individuals who are HLA-DRB1*15 carriers.

One of the pathways obesity might influence MS is through associations with vitamin D. Deficits of vitamin D and obesity might interact by modulating the immune system. Various studies have shown that overweight and obese individuals are more likely to be vitamin D deficient, possibly because of their metabolic clearance of vitamin D being faster than those with a normal body weight.[23] Sun exposure and vitamin D levels, particularly during childhood and early adolescence, have been linked to MS in a number of different studies.[6,24] Vitamin D's metabolite 25-hydroxyvitamin D was found to decrease development and stop progression of induced experimental autoimmune encephalomyelitis (EAE), the leading animal model of MS.[25] Another study showed that those who experienced low sun exposure during the ages of 6 and 15 years, especially during winter, had an earlier age at MS onset compared to those who had more sun exposure, a result that was much weaker or non-significant at a later age.[6] It is hypothesized that immune regulations play a role as vitamin D has immuno-modulating effects by inhibiting Th1 while having an agonistic effect on Th2.[26] Because the results from early-life vitamin D deficiency studies mimic our findings in overweight participants, it is conceivable that these factors are intricately related because of the increased metabolic clearance of vitamin D in overweight individuals.

The effect of early-life obesity on age at MS onset may also be caused by the adipocyte-derived hormone leptin. Adipose tissue secretes leptin in proportion to body fat mass and it serves to monitor fat storage and regulating food intake and systemic energy consumption. Leptin stimulates pro-inflammatory Th1 expression,[27] and leptin-deficient mice are unaffected by induced EAE.[28] A study investigating the effects of caloric restriction on EAE in mice found that it led to amelioration of clinical EAE with less severe inflammation and demyelination, and reduced concentrations of leptin.[29] As there are more women than men with MS, and there are indications that in recent years this gap is widening,[2] so is the serum concentration of leptin in women compared to men.[30] Next to its role in energy storage signaling, it also is involved in regulating the onset of puberty, with higher levels of leptin decreasing the age at menarche.[31] In light of this, females with MS were slightly younger at menarche compared to healthy controls.[14] The decreasing age at puberty onset, particularly in females, may contribute to the increased incidence and gender differences of MS among women. Potential biological mechanisms include prolonged exposure to higher levels of sex hormones or leptin. It has been proposed that metabolic factors such as childhood diet may lead to an earlier age at menstruation, as well as to altered leptin regulation (for example, through increased weight) which may contribute to MS disease development.[32]

Several factors are known to influence the risk of MS, including genetic predisposition, vitamin D deficiency, Epstein-Barr virus, smoking, menarcheal age, and obesity. None of these fully elucidate the risk of MS development, considering that most of these factors independently have very moderate effects. Therefore, interactions between, and additive effects of, risk factors are more likely to be of importance. Most studies suggest that weight, as well as other environmental factors, have little effect on MS risk when measured later in adulthood. In adulthood, higher weight had either no effect,[8] or even showed an inverse association with MS risk.[33] Therefore, it has been suggested by some authors that it could in fact be the loss of weight between adolescence and disease onset that may be a risk factor for MS.[33] This seems unlikely, as in our sample increased weight at both young adolescence as well as age 25 was associated with an earlier MS onset. Furthermore, those who had a higher weight at menarche were also likely to be of higher weight at age 25 (71% overlap), suggesting that most participants did not experience substantial weight loss. It therefore seems probable that there is a certain window of susceptibility in early life where weight can influence MS.

There are several limitations of this study. First, this retrospective study was based on a survey that did not initially set out to investigate weight and MS onset, and therefore limited information was available. Both weight and height were self-reported and relied on recollection. However, it has previously been shown that weight could be accurately recalled years to decades later,[34] and both recalled age at menarche and recalled body size at menarche were found to be well correlated with actual age and BMI at menarche.[35] Also, the sample consists only of women, and it is consequently difficult to generalize findings to men. BMI could not be computed at the time of first menstruation because height data were not collected at that time point. Therefore, analyses of BMI were limited to age 25. Although BMI takes into account both height and weight and is therefore a better measure of overall weight issues, BMI cannot distinguish between fat and muscle, nor can it distinguish between body compositions. Studies might benefit from recording body size information.

Our sample had a limited number of overweight and obese individuals, complicating the interpretation of these analyses. To address this issue, regression analyses using continuous measures of weight and BMI yielding similar results were also carried out. Future research should collect and analyze weight, height, and body size information at multiple time points in order to investigate the longitudinal dynamics weight may have on the development of MS leading to potentially identifying a window of susceptibility.

Previous studies have shown that weight in early life and young adulthood is a risk factor for developing MS. In the present study, we extend these findings to show that higher weight is associated with an earlier age at MS disease onset. Weight can generally be altered both through dietary changes and exercise, and it can therefore prove useful as one of the few modifiable risk factors.

Acknowledgements

The authors acknowledge members of the NYSMSC: Keith Edwards (MS Center of Northeastern NY Latham, NY), Andrew Goodman (University of Rochester Medical Center, Rochester, NY), Malcolm Gottesman (Winthrop Comprehensive MS Care Center, Mineola, NY), Joseph Herbert and Ilya Kister (NYU Langone Medical Center, New York, NY), Burk Jubelt (SUNY Upstate Medical University, Syracuse, NY), Patricia Coyle and Lauren Krupp (SUNY Stony Brook, Stony Brook, NY), Michael Lenihan (Adirondack Neurology Associates, PC, Glens Falls, NY), Allen Gerber (Albany Medical College, Albany, NY), Allan Perel (Alpha Neurology, PC, Staten Island, NY), Robert Zivadinov (Buffalo Neuroimaging Analysis Center, Deparment of Neurology, SUNY Buffalo, Buffalo, NY), and Carl Granger (Uniform Data Management for Rehabilitation, SUNY Buffalo, Buffalo, NY).

We would like to thank Mitchell Kopacz (Canisius College, Buffalo NY) for assisting with data entry and validation.

Conflicts of interest

Barbara Teter has received grant and or research support from Biogen Idec, Teva Neurosciences, EMD Serono, Avanir, Genzyme, and Novartis. Bianca Weinstock-Guttman has participated in speakers' bureaus and/or served as a consultant for Biogen Idec, Teva Neurosciences, EMD Serono, Pfizer, Novartis, Questcor, Genzyme, Mylan and Acorda. She has also received grant/research support from the agencies listed above as well as Shire.

Katelyn Kavak, Jesper Hagemeier, and Karen Zakalik have nothing to declare.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Warren SA, Svenson LW and Warren KG. Contribution of incidence to increasing prevalence of multiple sclerosis in Alberta, Canada. *Mult Scler* 2008; 14: 872–879.
2. Orton SM, Herrera BM, Yee IM, et al. Sex ratio of multiple sclerosis in Canada: A longitudinal study. *Lancet Neurol* 2006; 5: 932–936.
3. Cocco E, Sardu C, Lai M, et al. Anticipation of age at onset in multiple sclerosis: A Sardinian cohort study. *Neurology* 2004; 62: 1794–1798.
4. Masterman T, Ligers A, Olsson T, et al. HLA-DR15 is associated with lower age at onset in multiple sclerosis. *Ann Neurol* 2000; 48: 211–219.
5. Harbo HF, Isobe N, Berg-Hansen P, et al. Oligoclonal bands and age at onset correlate with genetic risk score in multiple sclerosis. *Mult Scler* 2014; 20: 660–668.
6. McDowell TY, Amr S, Culpepper WJ, et al. Sun exposure, vitamin D and age at disease onset in relapsing multiple sclerosis. *Neuroepidemiology* 2011; 36: 39–45.
7. Munger KL, Bentzen J, Laursen B, et al. Childhood body mass index and multiple sclerosis risk: A long-term cohort study. *Mult Scler* 2013; 19: 1323–1329.
8. Munger KL, Chitnis T and Ascherio A. Body size and risk of MS in two cohorts of US women. *Neurology* 2009; 73: 1543–1550.
9. Hedström AK, Olsson T and Alfredsson L. High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women. *Mult Scler* 2012; 18: 1334–1336.
10. Hedström AK, Lima Bomfim I, Barcellos L, et al. Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis. *Neurology* 2014; 82: 865–872.
11. Langer-Gould A, Brara SM, Beaber BE, et al. Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. *Neurology* 2013; 80: 548–552.
12. Wortsman J, Matsuoka LY, Chen TC, et al. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000; 72: 690–693.
13. Calder PC, Ahluwalia N, Brouns F, et al. Dietary factors and low-grade inflammation in relation to

overweight and obesity. *Br J Nutr* 2011; 106 (Suppl 3): S5–S78.

14. Ramagopalan SV, Valdar W, Criscuoli M, et al. Age of puberty and the risk of multiple sclerosis: A population based study. *Eur J Neurol* 2009; 16: 342–347.
15. Sloka JS, Pryse-Phillips WE and Stefanelli M. The relation between menarche and the age of first symptoms in a multiple sclerosis cohort. *Mult Scler* 2006; 12: 333–339.
16. Jacobs LD, Wende KE, Brownscheidle CM, et al. A profile of multiple sclerosis: The New York State Multiple Sclerosis Consortium. *Mult Scler* 1999; 5: 369–376.
17. World Health Organization. Obesity: Preventing and managing the global epidemic: Report of a WHO consulation. Geneva: World Health Organization, 2000.
18. Tomassini V and Pozzilli C. Sex hormones, brain damage and clinical course of multiple sclerosis. *J Neurol Sci* 2009; 286: 35–39.
19. Benedet J, da Silva Lopes A, Adami F, et al. Association of sexual maturation with excess body weight and height in children and adolescents. *BMC Pediatr* 2014; 14: 72.
20. Kurtzke JF, Hyllested K, Arbuckle JD, et al. Multiple sclerosis in the Faroe Islands. 7. Results of a case control questionnaire with multiple controls. *Acta Neurol Scand* 1997; 96: 149–157.
21. Anderson PM and Butcher KE. Childhood obesity: Trends and potential causes. *Future Child* 2006; 16: 19–45.
22. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002; 288: 1723–1727.
23. Rodríguez-Rodríguez E, Navia B, López-Sobaler AM, et al. Vitamin D in overweight/obese women and its relationship with dietetic and anthropometric variables. *Obesity (Silver Spring)* 2009; 17: 778–782.
24. Munger KL, Levin LI, Hollis BW, et al. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; 296: 2832–2838.
25. Lemire JM and Archer DC. 1,25-Dihydroxyvitamin D3 prevents the in vivo induction of murine experimental autoimmune encephalomyelitis. *J Clin Invest* 1991; 87: 1103–1107.
26. Smolders J, Damoiseaux J, Menheere P, et al. Vitamin D as an immune modulator in multiple sclerosis, a review. *J Neuroimmunol* 2008; 194: 7–17.
27. Matarese G, Carrieri PB, Montella S, et al. Leptin as a metabolic link to multiple sclerosis. *Nat Rev Neurol* 2010; 6: 455–461.
28. Matarese G, Di Giacomo A, Sanna V, et al. Requirement for leptin in the induction and progression of autoimmune encephalomyelitis. *J Immunol* 2001; 166: 5909–5916.
29. Piccio L, Stark JL and Cross AH. Chronic calorie restriction attenuates experimental autoimmune encephalomyelitis. *J Leukoc Biol* 2008; 84: 940–948.
30. Saad MF, Damani S, Gingerich RL, et al. Sexual dimorphism in plasma leptin concentration. *J Clin Endocrinol Metab* 1997; 82: 579–584.
31. Matkovic V, Ilich JZ, Skugor M, et al. Leptin is inversely related to age at menarche in human females. *J Clin Endocrinol Metab* 1997; 82: 3239–3245.
32. Bove R and Chitnis T. The role of gender and sex hormones in determining the onset and outcome of multiple sclerosis. *Mult Scler* 2014; 20: 520–526.
33. Markianos M, Evangelopoulos ME, Koutsis G, et al. Body mass index in multiple sclerosis: Associations with CSF neurotransmitter metabolite levels. *ISRN Neurol* 2013; 2013: 981070.
34. Troy LM, Hunter DJ, Manson JE, et al. The validity of recalled weight among younger women. *Int J Obes Relat Metab Disord* 1995; 19: 570–572.
35. Must A, Phillips SM, Naumova EN, et al. Recall of early menstrual history and menarcheal body size: After 30 years, how well do women remember? *Am J Epidemiol* 2002; 155: 672–679.