Environmental risk factors for multiple sclerosis in Japanese people

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Environmental risk factors for multiple sclerosis in Japanese people

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ABSTRACT

Background: The prevalence of multiple sclerosis (MS) has been increasing worldwide in recent years, especially among females. The same increasing trends are even observed in East Asian countries, where the prevalence of MS is relatively low compared with Northern European ancestries. Whether the environmental risk factors for MS are shared between Asian and North European ancestries, and the types of environmental factors that contribute to the low and recent increase in MS prevalence in Asian countries remain unknown. This study provides the first comprehensive survey of environmental risks for MS in East Asia.
Methods: Patients with MS were recruited from the Department of Neurology at Kyushu University Hospital, Japan between 01 April 2017 and 31 March 2018. Healthy controls (HCs) were recruited by public notification. All participants were residents of Kyushu Island and were required to complete medical history and lifestyle questionnaires. Dietary data were collected using a Food Frequency Questionnaire comprising intake of approximately 140 food and beverage items in the past 1 year. One hundred and three patients with MS and 124 healthy controls (HCs) completed the questionnaires. Age at onset and disability score measured by the Kurtzke Expanded Disability Status Scale (EDSS) were obtained from medical records.
Results: Frequency of obesity (body mass index $\geq$25 kg/m^2) at present time was higher in MS patients than in HCs (19.4% vs. 7.4%, p = 0.009), while body mass index at age 18–20 years did not differ between the two groups. Frequency of current or ex-smokers was higher in MS patients than in HCs (50.5% vs. 22.8%, p < 0.0001) and disability measured by the EDSS was more severe in MS patients with active smoking history than in patients without such history (p = 0.006 after adjusting for sex). Passive smoking after age 16 years was also a risk factor for MS (odds ratio: 1.31, 95% confidence interval: 1.05–1.63, p = 0.015). Longer sunlight exposure in early childhood was a protective factor for MS (odds ratio: 0.65 during summer and 0.71 during winter at age 6–10 years; 0.71 during summer and 0.72 during winter at age 11–15 years). MS patients had earlier age of menarche than HCs (mean: 12.4 years vs. 12.9 years, p = 0.031). Intake of grains was lower in MS patients than in HCs, with intake of rice in particular being significantly lower in MS patients than in HCs (mean: 235.2 g/day vs. 280.6 g/day, p = 0.006). Previously reported foods associated with MS in Northern European ancestries were not replicated in Japanese people.
Conclusion: Smoking and earlier age of menarche are positively associated and sunlight exposure in early childhood is negatively associated with MS in Japanese people as shown in Caucasians. Intake of steamed short-grain white rice, a staple food in Japan, is newly found to be negatively associated with MS in Japanese people. Although the causality is unclear because the participants were prevalent cases, these environmental factors may be involved in the rising prevalence of MS in Japanese females.

Abbreviations: BMI, body mass index; CI, confidence interval; CNS, central nervous system; EBV, Epstein–Barr virus; EDSS, Kurtzke Expanded Disability Status Scale; HCs, healthy controls; IM, infectious mononucleosis, MS, multiple sclerosis; MSSS, Multiple Sclerosis Severity Score; OR, odds ratio

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1. Introduction

Multiple sclerosis (MS) is caused by a complex interplay between genetic and environmental factors. It is considered that these genetic factors contribute about 30% of MS susceptibility, with the remaining susceptibility explained by environmental factors (Sadovnick et al., 1993). Thus, environmental factors have been extensively surveyed in Western countries, with high latitude, decreased sun exposure, vitamin D deficiency, early menarche, obesity in adolescence, smoking, and Epstein–Barr virus (EBV) infection identified as risk factors (Degelman et al., 2017; Duan et al., 2014; Jiang et al., 2018; Levin et al., 2010; Munger et al., 2009; Simpson et al., 2019; van der Mei et al., 2003).

In recent years, the prevalence of MS has been increasing worldwide, especially among females (Jiang et al., 2018). The same trend was confirmed by repeated nationwide surveys in Japan (Kuroiwa et al., 1975; Osoegawa et al., 2009; Shibasaki et al., 1992). The first nationwide survey carried out in 1972 revealed a very low MS prevalence (crude prevalence rate: 2.1/100,000) in Japan compared with those in countries predominantly comprising people of Northern European ancestry (Thompson et al., 2018), but the number of patients had increased by >20,000 cases (16.1/100,000) in the latest nationwide registration survey in 2017 (http://www.nanbyou.or.jp/entry/5354). The increase was more prominent in females (male-to-female ratio: 1:1.7 in the first nationwide survey and 1:2.9 in the fourth nationwide survey in 2004) (Kuroiwa et al., 1975; Osoegawa et al., 2009). The marked increase in MS prevalence may be explained by changes in exposure to environmental factors as well as alterations in interactions between environmental and genetic factors.

We previously reported that low 25-hydroxyvitamin D levels and EBV infection together with high latitude are risk factors, while *Helicobacter pylori* infection is a protective factor, for MS in Japanese people (Li et al., 2007; Nakamura et al., 2016; Niino et al., 2015; Yoshimura et al., 2012). However, very few environmental studies have been performed in Asian populations, including Japanese populations, whose lifestyles and genetic backgrounds differ from those of European people, and it thus remains largely unknown whether the established environmental risk factors for MS in Western populations are operative in Japanese populations. In the present study, we aimed to clarify the environmental factors for MS in Japanese people, which may account for the recent increase in MS prevalence in Japan, by performing a comprehensive environmental survey.

2. Patients and methods

2.1. Subjects

Japanese patients with MS who were regularly followed-up at the Department of Neurology, Kyushu University Hospital between 01 April 2017 and 31 March 2018 were eligible for inclusion. Patients were included if they met the McDonald criteria for MS (Polman et al., 2011), were at least 20 years of age, could answer the questionnaires by themselves, and signed the informed consent form. Healthy controls (HCs) were recruited by public notification. A total of 103 MS patients and 124 HCs were enrolled in the study. All participants were Japanese people residing in the northern parts of Kyushu Island, Japan, at approximately 130° east longitude and 33° north latitude. Age at examination and sex ratio did not differ significantly between MS patients and HCs (Table 1). The study was approved by the Kyushu University Ethics Committee and conducted according to the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. Data collection

All participants were requested to answer self-reported questionnaires including present and past lifestyles and medical history. The questionnaires concerning lifestyle and medical history included age, sex, height, body weight, body weight at age 18–20 years, birthplace, current place of residence, history and periods of living overseas, education level, occupation, medical history including atopy/allergy and infectious mononucleosis (IM), family history of MS or neuromyelitis optica spectrum disorders, history of being breastfed as a child, detailed smoking history (ever smoked, age started/stopped smoking, amount of smoking per day, history of passive smoking), and sunlight exposure. Participants were asked to provide the period (0–15 or ≥16 years) and frequency (rare, several times a month, several times a week, almost every day) of exposure to passive smoking exceeding 1 h per day. For sunlight exposure, participants were requested to choose a duration of sun exposure (<15, 15–29, 30–59, 60–89, or ≥90 min daily) in summer and winter for different age periods (6–10, 11–15, 16–20, and ≥21 years). For female participants, history of pregnancy, childbirth, and breastfeeding, age at menarche, and use of oral contraceptives or infertility medications were also asked.

Participants were requested to fill out a Food Frequency Questionnaire to elucidate their recent dietary habits in the past 1 year for frequency of intake of approximately 140 food and beverage items (Nanri et al., 2012; Willett et al., 1985). The questionnaire comprised two categories. The first category addressed eating frequency. For most food items, nine possible options could be selected: ‘less than once per month’, ‘1 to 3 times per month’, ‘1 to 2 times per week’, ‘3 to 4 times per week’, ‘5 to 6 times per week’, ‘once a day’, ‘2 to 3 times per day’, ‘4 to 6 times per day’, and ‘7 or more times per day’. The second category assessed intake relative to appropriate standard portion sizes selected for each food item. The questionnaire used words and pictures to show the standard portion sizes for each food item, and three options could be chosen: ‘less than half the standard portion size’, ‘same as the standard portion size’, or ‘more than 1.5 times the standard portion size’. Age at MS onset and disability measured by the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) were collected from medical records and the Multiple Sclerosis Severity Score (MSSS) (Roxburgh et al., 2005) was estimated from the clinical information.

2.3. Data management

The information gathered by the Food Frequency Questionnaire was used to estimate the daily intake of ingredients and components. The participants were classified as with or without active smoking history based on their answer to the question of whether they had ever smoked. In terms of passive smoking and sunlight exposure, the answers were categorized into ordinal scales (1–4 and 1–5, respectively) and the scales were used as objective variables in a logistic regression model. The correlations between environmental factors and disability were examined in all patients and after exclusion of patients with ≤5 years of disease duration, because disability at 5 years after onset was shown to be a prognostic factor and the clinical course and disability in the early disease course fluctuate largely on a case-by-case basis (Degenhardt et al., 2009).

2.4. Statistical analysis

Fisher's exact test was used to compare categorical variables, and the Wilcoxon rank-sum test was used to analyse continuous variables. The Spearman rank-correlation coefficient was used to evaluate the correlations between disease severities (EDSS score and MSSS) and pack-years of smoking. Univariate logistic regression analyses were performed to estimate the odds ratio (OR) of individual environmental factors, and a multivariable logistic regression analysis was subsequently conducted with inclusion of all associated factors as covariates. EDSS scores and MSSS were rank-normalized and applied to linear regression analysis. The threshold for statistical significance was set at $p < 0.05$. Statistical analyses were performed using JMP Pro 14.1.0

Table 1
Demographic and clinical characteristics of MS patients and HCs.

	MS patients (n = 103)	HCs (n = 124)	p-value
Age at examination (years), mean ± SD (range)	43.6 ± 10.9 (21–71)	40.7 ± 13.4 (20–68)	NS
Females / males, *n* (%)	80 / 23 (77.7 / 22.3)	88 / 36 (71.0 / 29.0)	NS
Allergy or atopic dermatitis, *n* (%)	48 (47.1)	46 (37.7)	NS
Past history of infectious mononucleosis, *n* (%)	0 (0)	1 (0.8)	NS
Family history of MS or NMOSD, *n* (%)	3 (2.9)	0 (0.0)	NS
RRMS : SPMS : PPMS, *n*	82 : 14 : 7	NA	NA
Disease duration (years), mean ± SD (range)	13.0 ± 8.6 (1–42)	NA	NA
EDSS score, mean ± SD (range)	2.85 ± 2.22 (0–8.0)	NA	NA
MSSS, mean ± SD (range)	3.35 ± 2.92 (0.05–9.38)	NA	NA
Weight (kg), mean ± SD (range)	56.6 ± 11.2 (38–95)	56.1 ± 9.5 (41–90)	NS
Height (cm), mean ± SD (range)	160.2 ± 6.77 (147–176)	161.8 ± 8.29 (149–184)	NS
BMI (kg/m^2), mean ± SD (range)	22.0 ± 4.03 (14.8–36.3)	21.3 ± 2.80 (16.4–37.0)	NS
BMI at age 18–20 years, mean ± SD (range)	20.6 ± 3.64 (15.8–31.3)	20.4 ± 2.08 (16.2–28.4)	NS
BMI ≥25 kg/m^2 at age 18–20 years, *n* (%)	7 (6.9)	3 (2.5)	NS
BMI ≥25 kg/m^2, *n* (%)	20 (19.4)	9 (7.4)	0.010
Active smoking history, *n* (%)	52 (50.5)	28 (22.8)	<0.0001
Pack-years, mean ± SD (range)	11.1 ± 8.91 (0.15–37)	14.2 ± 13.4 (0.03–48.8)	NS
Breastfeeding, *n* (%)	47 (45.6)	63 (51.6)	NS

BMI: body mass index; EDSS: Kurtzke Expanded Disability Status Scale; HCs: healthy controls; MS: multiple sclerosis; NA: not applicable; NMOSD: neuromyelitis optica spectrum disorders; NS: not significant; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis.

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software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Participant demographics

The demographic features of the MS patients and HCs are shown in Table 1. Among the MS patients, 79.6% had a relapsing-remitting course and the rest had a progressive course (13.6% with a secondary progressive course and 6.8% with a primary progressive course). The median current EDSS score was 2.85 and the mean disease duration was 13.0 years. There were no significant differences in age at examination, sex ratio, history of atopy/allergy, IM, breastfeeding, and family history of MS and neuromyelitis optica spectrum disorders between MS patients and HCs. There were no significant differences in weight, height, and body mass index (BMI) at either present time or age 18–20 years between MS patients and HCs. However, frequency of obesity (BMI ≥25 kg/m^2) at present time was higher in MS patients than in HCs, and the OR was 3.03 (95% confidence interval [CI]: 1.31–6.98, p = 0.010). Frequency of obesity at age 18–20 years did not differ between MS patients and HCs.

3.2. Smoking

Active smoking history was significantly more frequent in MS patients than in HCs (Table 1), and its OR was 3.46 (95% CI: 1.95–6.13, p < 0.0001). Even when three MS patients who started active smoking after onset of MS were excluded, the result was essentially the same (OR: 3.26, 95% CI: 1.83–5.80, p < 0.0001). The result still remained the same when four additional patients who started active smoking at <1 year prior to diagnosis of MS were excluded (OR: 3.00, 95% CI: 1.67–5.36, p = 0.0002) (Fig. 1A). Exposure to passive smoking after age 16 years was also significantly more frequent in MS patients than in HCs (OR: 1.31, 95% CI: 1.05–1.63, p = 0.015) (Fig. 1B).

3.3. Sunlight exposure

Duration of sun exposure at ages 6–10 and 11–15 years in both winter and summer was significantly shorter in MS patients than in HCs (Fig. 2). For age 6–10 years, the OR was 0.65 (95% CI: 0.47–0.90, p = 0.007) during summer and 0.71 (95% CI: 0.53–0.95, p = 0.020) during winter. For age 11–15 years, the OR was 0.71 (95% CI: 0.53–0.96, p = 0.025) during summer and 0.72 (95% CI: 0.54–0.97, p = 0.030) during winter (Fig. 2). When males and females were analysed separately, the trend remained significant until age 20 years in females during winter (OR: 0.74 95% CI: 0.56–0.98, p = 0.033), while only a tendency was observed during summer (OR: 0.76, 95% CI: 0.56–1.02, p = 0.066).

3.4. Female-specific variables

Age at menarche was significantly lower in MS patients than in HCs (mean ± SD: 12.4 ± 1.46 years vs. 12.9 ± 1.48 years, p = 0.031) (Table 2). One-year-delayed menarche was negatively associated with MS (OR: 0.80, 95% CI: 0.65–0.99, p = 0.042). When we excluded four patients who had menarche after onset of MS or <1 year prior to diagnosis of MS, the trend was more evident (OR: 0.77 95% CI: 0.61–0.96, p = 0.016). Pregnancy, number of pregnancies, age at first pregnancy, birth, number of births, age at first birth, and usage of infertility medications or oral contraceptives did not differ significantly between MS patients and HCs. However, birth (44.3% vs. 61.4%, p = 0.031) and number of births (0.95 vs. 1.35, p = 0.033) were significantly lower in MS patients than in HCs.

3.5. Dietary habits

Among the examined food groups, only intake of grains was significantly lower in MS patients than in HCs (342.8 ± 57.9 g/day vs. 364.8 ± 77.6 g/day, p = 0.021) (Table 3). Among the grain ingredients, intake of steamed short-grain white rice was significantly lower in MS patients than in HCs (235.2 ± 121.0 g/day vs. 280.6 ± 113.6 g/day, p = 0.006), while intake of soba was significantly higher in MS than in HCs (12.7 ± 15.1 g/day vs. 9.9 ± 16.8 g/day, p = 0.030) (Table 4). Dietary consumption of some foods and ingredients reported to be associated with MS susceptibility in people of Northern European ancestry after interviews with participants using the recall method, such as fish, coffee, n-3 fatty acids, vitamin D, salt, and alcohol (Andersen et al., 2018; Bäärnhielm et al., 2014; Duan et al., 2014; Farez et al., 2015; Hedström et al., 2016a; Hoare et al., 2016), did not differ significantly between MS patients and HCs.

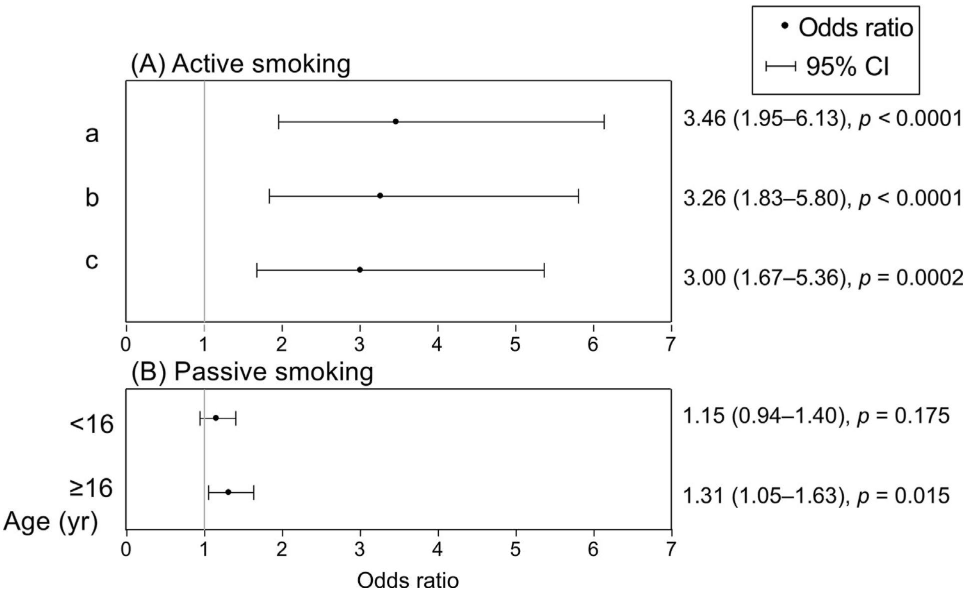

Fig. 1. Relationship between smoking history and MS risk. (A) Association between active smoking history and MS. (a) Results of an analysis including all participants. (b) Results of an analysis with exclusion of three MS patients who started active smoking after onset of MS. (c) Results of an analysis with exclusion of four additional patients who started active smoking at <1 year prior to diagnosis of MS. (B) Association between passive smoking history and MS. The question for passive smoking was "How long have you had the opportunity to inhale environmental cigarette smoke from other people for more than 1 h a day at home or at work?". In terms of passive smoking history, the answers were categorized into an ordinal scale (1–4) and the scales were used as objective variables in a logistic regression model. Exposure to passive smoking at age ≥16 years is a risk factor for MS with an OR of 1.31.

3.6. Multivariable logistic regression analysis

In the multivariable logistic regression analysis with sunlight exposure at young age, active smoking history, passive smoking history after age 16 years, intake of rice, and intake of soba as covariates, active smoking history and intake of rice remained significant ($p = 0.003$ and $p = 0.028$, respectively). Even when female MS patients and HCs were analysed with inclusion of female-specific variables (age at menarche, birth, number of births), active smoking history and age at menarche were still significant ($p = 0.025$ and $p = 0.038$, respectively).

3.7. Correlation with disease severity

EDSS scores and MSSS were significantly greater in MS patients with active smoking history than in those without such history, regardless of whether the analysis involved all patients or patients after exclusion of those with ≤5 years of disease duration (Fig. 3 and Supplementary Table 1). However, disease severity was not correlated with pack-years of smoking (EDSS score: $\rho = 0.240$, $p = 0.094$; MSSS: $\rho = 0.242$, $p = 0.090$). When high rice eaters were defined as those with equal to or more than the median amount of rice intake in HCs (≥280 g/day) and low rice eaters were defined as those with equal to or less than half the median amount of rice intake in HCs (≤140 g/day), high rice eaters had significantly lower MSSS ($p = 0.034$) and frequency of progressive MS ($p = 0.0004$) and a tendency toward lower EDSS scores ($p = 0.057$) than low rice eaters in MS patients excluding those with ≤5 years of disease duration (Fig. 4 and Supplementary Table 2).

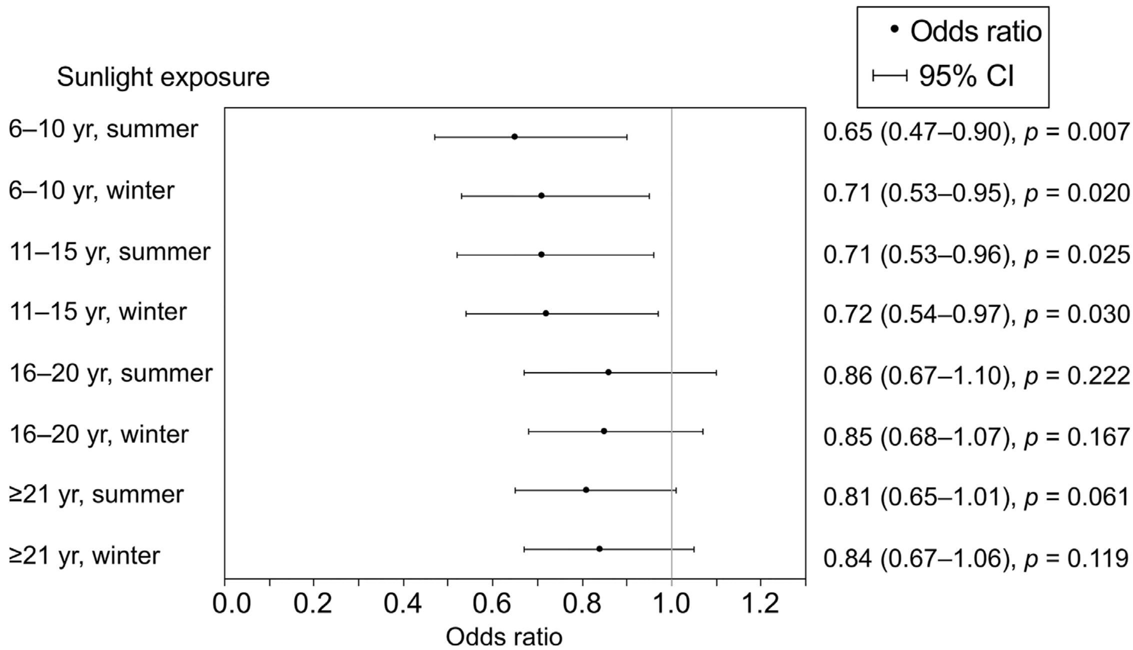

Fig. 2. Relationship between sunlight exposure and MS risk. Duration of sun exposure at age <16 years is associated with MS susceptibility. In terms of sunlight exposure, the answers were categorized into an ordinal scale (1–5) and the scales were used as objective variables in a logistic regression model. Increasing sun exposure is associated with decreasing risk of MS.

Table 2
Female-specific variables.

	MS patients (n = 80)	HCs (n = 88)	p-value
Age at menarche (years), mean ± SD (range)	12.4 ± 1.46 (10–18)	12.9 ± 1.48 (10–18)	0.031
Pregnancy, *n* (%)	43 (54.4)	55 (63.2)	NS
Number of pregnancies, mean ± SD (range)	1.33 ± 1.39 (0–5)	1.66 ± 1.69 (0–8)	NS
Age at first pregnancy (years), mean ± SD (range)	26.3 ± 5.33 (18–38)	27.1 ± 4.88 (16–39)	NS
Birth, *n* (%)	35 (44.3)	54 (61.4)	0.031
Number of births, mean ± SD (range)	0.95 ± 1.09 (0–4)	1.35 ± 1.16 (0–4)	0.033
Age at first birth (years), mean ± SD (range)	27.2 ± 4.86 (19–39)	28.0 ± 4.65 (17–39)	NS
Infertility medicine usage, *n* (%)	8 (10.0)	7 (8.0)	NS
Oral contraceptive usage, *n* (%)	4 (5.0)	2 (2.3)	NS

HCs: healthy controls; MS: multiple sclerosis; NS: not significant; SD: standard deviation.

4. Discussion

This study showed that active smoking, passive smoking, and menarche at earlier age were associated with MS susceptibility, while longer sun exposure at younger age was a protective factor against MS, in Japanese people, as also seen for MS in people of Northern European or Middle Eastern ancestry (Degelman et al., 2017; Hedström et al., 2016b; Jiang et al., 2018; van der Mei et al., 2003). However, BMI at early age and consumption of foods known to be associated with MS did not differ between MS patients and HCs in the Japanese population. As a novel factor in the Japanese population, rice consumption was significantly lower in MS patients than in HCs.

There are several limitations to this study. First, the sample size was relatively small, and the cases were hospital-based and at various clinical stages, mainly because of the low prevalence of MS in the Japanese population (Osoegawa et al., 2009). This may have produced some selection bias and heterogeneity in the MS patients evaluated. Second, because the study used self-reported questionnaires, recall biases could be large particularly in MS patients with long disease durations. Third, the study investigated current food intake, and MS patients may have changed their dietary lifestyle after receiving their diagnosis. Some of the associations of environmental factors with MS including the associations between dietary factors and MS, and between active smoking and disability could be due to reverse causality. Thus, the present findings should be regarded as preliminary. Furthermore, there were no MS patients who reported IM in their past history. Although IM is an established risk factor for MS in European ancestries (Sheik-Ali, 2017), the lower prevalence of IM in Japanese compared with Caucasians (Takeuchi et al., 2006) may partly explain this observation. Future large-scale prospective studies are warranted to clarify the causality of the environmental factors associated with MS in Japanese.

Smoking is a well-established risk factor for MS in Caucasian people (Degelman et al., 2017). In experimental autoimmune encephalomyelitis, an animal model of MS, autoimmune T cells were shown to become eligible for invasion of the central nervous system (CNS) after activation in the pulmonary hilar lymph nodes (Odoardi et al., 2012). Smoking renders the pulmonary hilar lymph nodes pro-inflammatory, and can thus exacerbate CNS inflammation in MS (Alrouji et al., 2019). Indeed, active smoking was associated with greater disability in the present study, suggesting a contribution of smoking to disability progression via augmented neuroinflammation. Although smoking frequency in the total population is decreasing in Japan consistent with worldwide trends, the smoking frequency in females aged in their 20 s increased from 1988 to 2003 (http://www.health-net.or.jp/tobacco/product/pd090000.html). Therefore, increasing smoking frequency in young women may be contributing to the rising prevalence of MS in Japanese females at the present time.

Regarding female-specific variables, earlier menarche was identified as a common risk factor for MS in Caucasians (Jiang et al., 2018) and the present Japanese MS patients, and produces longer exposure to female sex hormones. Oestrogen, a female hormone, dampens cell-mediated immune function, but enhances humoral-mediated immune function (Foo et al., 2017). The recent success of B-cell depletion therapy for MS (Hauser et al., 2017) suggests the importance of humoral immunity for MS pathogenesis, and the earlier exposure to sex hormones may increase susceptibility to MS via augmentation of humoral immunity. Age at menarche continues to decrease worldwide in advanced countries including Japan (Hosokawa et al., 2012; Ysrraelit and Correale, 2019). Thus, menarche at younger age is likely to have contributed to the recent increase in MS prevalence among females in Japan. The significantly lower frequencies of birth and

Table 3
Intake of food groups.

Food group (g/day)	MS patients (n = 103)	HCs (n = 124)	p-value
Grains, mean ± SD (range)	342.8 ± 57.9 (255–596)	364.8 ± 77.6 (283–719)	0.021
Potatoes, mean ± SD (range)	43.0 ± 8.3 (29–102)	41.5 ± 4.8 (29–61)	NS
Beans, mean ± SD (range)	78.0 ± 47.3 (47–384)	71.8 ± 27.2 (41–237)	NS
Seeds, mean ± SD (range)	1.7 ± 4.0 (0–30.3)	2.0 ± 4.7 (0–30.5)	NS
Vegetables, mean ± SD (range)	349.7 ± 54.4 (265–568)	351.8 ± 77.1 (255–1002)	NS
Fruits, mean ± SD (range)	157.4 ± 24.4 (114–233)	154.5 ± 23.9 (114–238)	NS
Mushrooms, mean ± SD (range)	22.4 ± 27.6 (10–286)	20.7 ± 13.2 (10–123)	NS
Seaweeds, mean ± SD (range)	10.4 ± 4.8 (8–48)	10.3 ± 2.8 (8–25)	NS
Seafoods, mean ± SD (range)	88.6 ± 15.0 (74–173)	88.2 ± 11.5 (74–125)	NS
Meats, mean ± SD (range)	80.2 ± 26.2 (41–177)	81.8 ± 26.0 (44–211)	NS
Eggs, mean ± SD (range)	34.5 ± 7.4 (28–80)	34.3 ± 7.7 (27–111)	NS
Milk, mean ± SD (range)	175.8 ± 60.9 (102–479)	171.3 ± 64.5 (103–451)	NS
Fats and oils, mean ± SD (range)	13.7 ± 12.9 (1.4–82.0)	12.0 ± 7.2 (0.4–38.5)	NS
Sweets, mean ± SD (range)	28.9 ± 24.4 (0–111.1)	28.1 ± 28.5 (0–195.8)	NS
Beverages (tea, coffee, juice, carbonated drink), mean ± SD (range)	819.9 ± 664.1 (0–4925)	745.7 ± 478.0 (25.7–2425.7)	NS
Alcohol, mean ± SD (range)	91.1 ± 147.2 (19–1031)	101.7 ± 155.0 (19–897)	NS
Seasoning and spices, mean ± SD (range)	18.1 ± 12.2 (0.4–61.7)	18.3 ± 13.1 (0.3–65.2)	NS

HCs: healthy controls; MS: multiple sclerosis; NS: not significant; SD: standard deviation.

Table 4
Intake of ingredients included in grains.

Ingredient (g/day)	MS patients (n = 103)	HCs (n = 124)	p-value
Rice, mean ± SD (range)	235.2 ± 121.0 (55–560)	280.6 ± 113.6 (55–560)	0.006
Wheat, mean ± SD (range)	143.4 ± 113.8 (2–653)	148.7 ± 98.8 (13–600)	NS
Soba (buckwheat noodles), mean ± SD (range)	12.7 ± 15.1 (0–64)	9.9 ± 16.8 (0–100)	0.030

HCs: healthy controls; MS: multiple sclerosis; NS: not significant; SD: standard deviation.

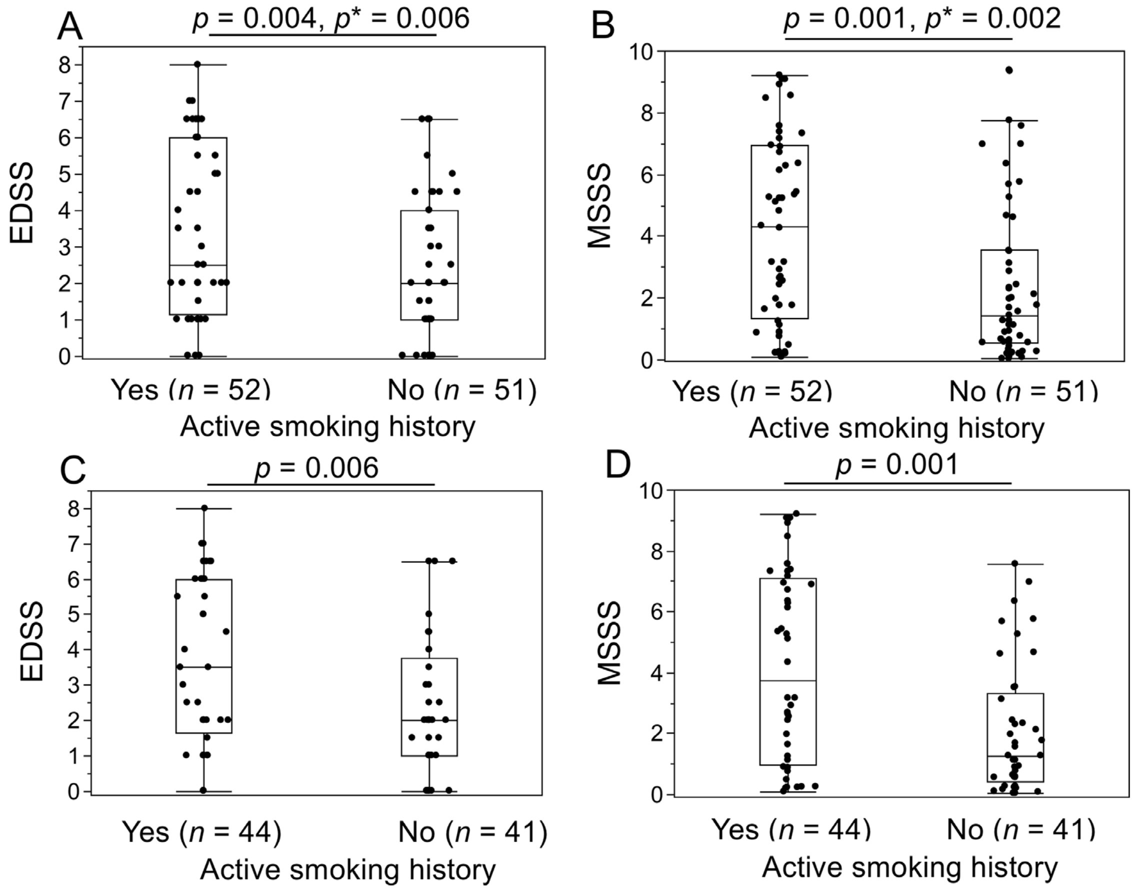

Fig. 3. Disease severity according to active smoking history. (A, B) Data for all MS patients (n = 103). (C, D) Data for MS patients excluding those with ≤5 years of disease duration (n = 85). For active smoking history, we classified the participants into two groups based on their answer to the question of whether they had ever smoked. The mean values remain higher in patients with active smoking history after adjustment for sex in a multivariable linear regression analysis on all MS patients. p^* indicates p-value adjusted for sex (because a significant difference for sex was found during analyses on age at examination, sex, and disease duration by presence or absence of active smoking history). The same result is obtained when those with ≤5 years of disease duration are excluded.

number of births in MS patients compared with HCs are compatible with previous studies reporting that number of births is protective for MS (Magyari et al., 2013; Ponsonby et al., 2012). However, the difference was not significant by multivariable logistic regression analysis. Because pregnancies and births can be influenced by MS itself, the interpretation of causality awaits future larger-scale studies.

Although our Japanese MS patients did not replicate the associations of several foods reported to be risk or protective factors for MS, we found that intake of steamed short-grain white rice, a staple Japanese food, was a novel protective factor for MS in Japanese people. Intriguingly, MS prevalence is generally low in counties where rice is a staple food, including Japan, China, Thailand, Indonesia, and India. It is possible that rice consumption may partly influence the worldwide tendency for MS prevalence. The consumption of rice among Japanese people has decreased by half in the past 40 years, while the consumption of meat has dramatically increased (http://www.maff.go.jp/j/wpaper/w_maff/h18_h/trend/1/t1_1_1_04.html). These changes in dietary habits may have partly contributed to the increasing MS prevalence in Japanese people since World War II.

It is possible that Westernization of the diet may confer MS susceptibility by increasing the frequency of obesity in younger Japanese generations, because a previous study demonstrated that early childhood obesity and adolescent obesity were risk factors for MS susceptibility (Munger et al., 2009). However, in our series, the mean BMI at age 18–20 years was 20.6 kg/m^2 in MS patients and comparable to the value in the nationwide survey. Indeed, the nationwide survey in Japan reported that BMI at age 17–19 years in females remained stable at around 20 kg/m^2 from 1976 to 2016 (http://www.nibiohn.go.jp/eiken/kenkounippon21/eiyouchousa/keinen_henka_shintai.html). The higher frequency of current obesity (BMI ≥25 kg/m^2) in MS patients compared with HCs could be attributable to the reduced mobility or steroid usage in some patients, because BMI and frequency of obesity at age 18–20 years and BMI at examination did not differ significantly between MS patients and HCs. Thus, obesity does not seem to be a major driving factor for MS in Japanese people, although dietary habits have markedly changed.

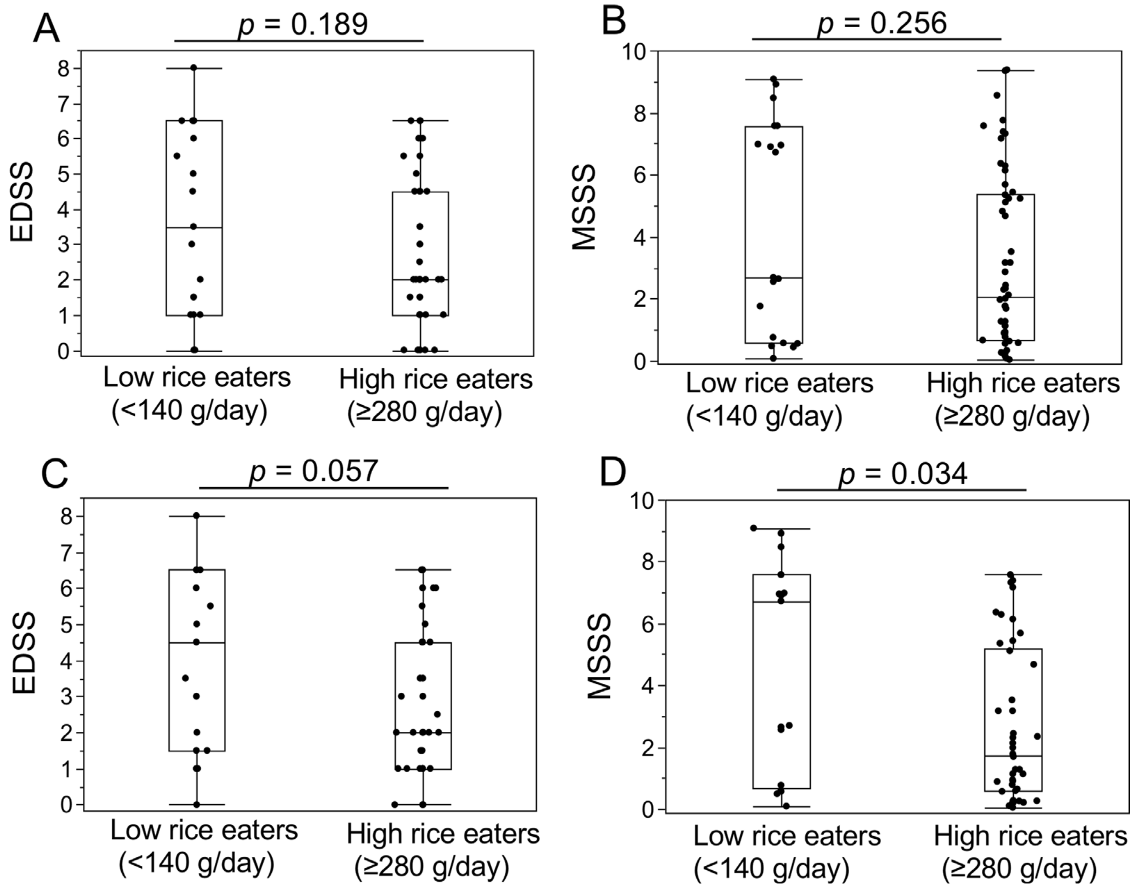

Fig. 4. Disease severity according to rice intake. (A, B) Data for all MS patients ($n = 54$ for high rice eaters; $n = 19$ for low rice eaters). (C, D) Data for MS patients excluding those with ≤5 years of disease duration ($n = 42$ for high rice eaters; $n = 17$ for low rice eaters). High rice eaters were defined as those with equal to or more than the median amount of rice intake in HCs (≥280 g/day) and low rice eaters were defined as those with less than half the median amount of rice intake in HCs (<140 g/day). High rice eaters show significantly lower MSSS ($p = 0.034$) and a tendency toward lower EDSS scores ($p = 0.057$) than low rice eaters in MS patients excluding those with ≤5 years of disease duration.

Several etiological pathways other than obesity are plausible for the mechanism of rice consumption as a protective factor against MS. First, glucan included in rice has a protective effect for allergies and autoimmune diseases (Oomizu et al., 2006). Differentiation of immune cells toward cells with anti-inflammatory properties after exposure to glucan may reduce the risk of MS (Oomizu et al., 2006). Second, gut commensal bacteria and their metabolites have the potential to exert both pro-inflammatory and anti-inflammatory responses by regulating T-cell differentiation and immune responses in the gut (Furusawa et al., 2013). Therefore, much attention has recently been paid to the relationships between MS and gut microbiota. Intestinal microbial flora become altered in a relatively short time after a change in the staple food. The *Blautia* genus is increased by consumption of rice (Mano et al., 2018). Thus, Japanese people have an abundance of this genus compared with people in other countries (Nishijima et al., 2016). Interestingly, a recent report described that the *Blautia* genus was decreased in Japanese MS patients (Miyake et al., 2015), consistent with the lower rice intake in MS patients noted in the present study. Therefore, decreased rice consumption may have changed the gut microbiota, such as *Blautia* species, thereby potentiating the MS risk in Japanese people. However, in North American people, *Blautia* species were reported to be more abundant in MS patients than in HCs (Chen et al., 2016). Thus, the relationships between food intake and gut microbiota in MS may be distinct among races with different dietary habits.

5. Conclusion

Our comprehensive study on environmental factors for MS identified smoking, earlier age of menarche, and low sunlight exposure as environmental risk factors in Japanese people, similar to Western people. We also found a negative association of rice intake with MS, which may be unique to Japanese people. We consider that the identification of environmental risk factors for MS among races will lead to elucidation of the disease cascade.

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Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.101872.

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