**Supplemental Material**

***Impact of Sex on Clinical Outcome in early Multiple Sclerosis***

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**Supplemental Methods I:** The Nine-Hole Peg Test is a standardized assessment tool used to evaluate fine motor skills and hand dexterity. It involves placing nine pegs into nine holes on a pegboard, and then removing them as quickly as possible. The patient is given a block with nine empty holes and nine pegs. The subject is instructed to place the pegs into the holes one at a time, using only one hand, as quickly as possible. Once all nine pegs have been placed, the subject is instructed to remove them one at a time, again using only one hand and as quickly as possible. Two trials with the dominant hand are followed by two trials with the non-dominant hand. Time to complete the task is measured in seconds. The 9HPT scores range from 0 to 300 seconds. The average time for each hand is calculated. Both assessments (i.e. one assessment for each side) are being used as outcome measure. (1)

**Supplemental Methods II:** The Timed 25-Foot Walk Test is a standardized assessment tool used to evaluate mobility and gait speed. It involves measuring the time it takes for an individual to walk 25 feet as quickly and safely as possible. The test is typically conducted in a hallway or other level, unobstructed space that is at least 25 feet long. The subject is instructed to stand at one end of the space and walk as quickly and safely as possible to the other end. Time in seconds for the subject to complete the walk is recorded. Possible T25FW scores range from 0 to 180 seconds. The test is performed twice and the average is calculated. (2)

**Supplemental Methods III:** Cognitive function is assessed with the Brief Repeatable Battery of Neuropsychiatric Tests (BRB-N).(3) The BRB-N consists of five subtests of which each assesses different cognitive domains:

The Selective Reminding Test (SRT) assesses verbal learning and long-term memory storage. The examiner reads one word of a list of 12 every two seconds, and the patient under assessment is requested to remember all 12 words. The test consists of six trials. On each trial, the participant is presented with only the words that were omitted in the previous trial. We distinguish Long Term Storage (SRT-LTS) and Consistent Long-Term Retrieval (SRT-CLTR). If the word was remembered in two consecutive trials, the patient scores a point for SRT-LTS. If the word is remembered in at least two trials and continuously until the last trail, the patient scores a point for SRT-CLTR. For each trail (1-6) we calculate both the LTS and the CLTR score column wise. We add all six single values to a total SRT-LTS and SRT-CLTR score. After 15 minutes, the participant is asked to recall the 12-word list. (SRT-DR) Maximum test scores to be reached are 72 for SRT-LTS and SRT-CLTR and 12 for SRT-DR. (3, 4)

The 10/36 Spatial Recall Test (SPAT) measures visuospatial learning and delayed recall. It is composed of a 6 × 6 chessboard with 10 randomly placed pieces. The chessboard-pattern is presented to the participant for 10 seconds. After, the tested person tries to reproduce the original pattern on a blank board. This task is repeated twice (SPAT 1-3). 15 min later, the subject is asked to recall the pattern again in a delay-recall trial (SPAT-DR). Correct responses are counted for each trial (SPAT1-3) and added to the final score. The SPAT-DR score is calculated separately.

Maximum test score to be achieved for SPAT1-3 is 30 and 10 for the SPAT-DR. (3)

The Symbol Digit Modalities Test (SDMT) examines information-processing speed, visual working memory and concentration. The participant views nine simple geometric symbols. The symbols are labeled from 1 to 9. The patient has 90 seconds to replace the symbols verbally with the corresponding number. The participant is asked to proceed row by row. The final score is the number of correct replacements. Maximal test score is 110. (5, 6)

The Paced Auditory Serial Addition Test-3 (PASAT3) measures concentration, thinking speed and calculation ability speed. In this test, a series of numbers from 1 to 9 are presented every three seconds. The participant is asked to add the numbers heard in pairs, while ignoring the result of the previous addition. The test score results from the number of correct answers. Maximal test score, that the participant can reach, is 60. (3, 7)

The Word List Generation test (WLG) examines semantic-categorical word fluency, verbal drive, and category formation (belongs to executive functions). A category is given by the examiner and within 90 seconds the patient should name as many different words as possible that fit this category. The final score of the test is the number of correct answers given by the patient (without repetitions or inappropriate terms). (3, 8)

**Supplemental Methods IV:** The Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) consists of 38 items, of which 28 are the basis for the computation of five subscale scores (fatigue, lower limb function, upper limb function, social function, and mood). Each item is scored from 1 to 5. High scores indicate low quality of life. A total score can be calculated by averaging the five subscale scores. (9)

**Supplemental Methods V:** The Short Form 36 (SF36) is a health-related quality of life questionnaire that measures an individual's general health status. It assesses eight health domains, including physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health.

The SF36 questionnaire consists of 36 questions. Each question has multiple response options, and the answers are assigned scores ranging from 0 to 100, with higher scores indicating better health status. (10)

**Supplemental Methods VI:** The Fatigue Severity Scale (FSS) is a questionnaire assessing the severity of fatigue in individuals with various health conditions. It consists of nine questions that measure the impact of fatigue on a person's ability to function in their daily activities. The FSS requests to rate one’s level of agreement with statements related to one’s experience of fatigue over the past week, such as "My fatigue prevents sustained physical functioning" and "My fatigue interferes with carrying out certain duties and responsibilities." Each statement is rated on a scale of 1 to 7, with 1 indicating strong disagreement and 7 indicating strong agreement. The total score is calculated as mean score. The total mean FSS score ranges from 1 to 7, with higher scores indicating greater severity of fatigue. (11)

**Supplemental Methods VII:** The FSMC consists of 20 questions divided into two parts: the motor subscale and the cognitive subscale, which was validated in an MS population. The motor subscale includes questions related to physical fatigue, such as difficulty with walking or arm movements. The cognitive subscale includes questions related to mental fatigue, such as difficulty with concentration or memory. Each question on the FSMC is rated on a scale of 1 to 5, with 1 indicating no fatigue and 5 indicating severe fatigue. The total score on the FSMC ranges from 20 to 100, with higher scores indicating greater levels of fatigue. (12)

**Supplemental Methods VIII:** The Beck Depression Inventory II (BDI-II) is a widely used self-report questionnaire that is designed to measure the severity of depressive symptoms in individuals. It consists of 21 questions that assess a range of symptoms related to depression, including feelings of sadness, loss of interest in activities, changes in sleep and appetite, feelings of guilt or worthlessness, and suicidal ideation. Each question on the BDI-II is scored on a scale of 0 to 3, with higher scores indicating greater severity of symptoms. The total score on the BDI-II ranges from 0 to 63, with scores of 0-13 indicating minimal depression, scores of 14-19 indicating mild depression, scores of 20-28 indicating moderate depression, and scores of 29-63 indicating severe depression. (13)

**Supplemental Results I:** As a sensitivity analysis we explored whether the number of examinations differed between female and male patients. We examined the number of test participations. Females had 399 PASAT3 and 348 SDMT tests in total (PASAT3 test participation: mean=4.11, SD=1.62, SDMT test participation: mean=3.59, SD=1.34) and males 207 PASAT3 and 180 SDMT tests in total (PASAT3 test participation: mean=3.98, SD=1.65, SDMT test participation: mean=3.46, SD=1.46) indicating no systematic differences in the number of conducted tests.

**Supplemental Table I: Overview - research questions with sample sizes and timepoints of data assessment**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Sub-question** | **Number of participants** | **Timepoint of data assessment** |
| **Relapses** | TTR | 149 | Baseline to 4FU |
| **Disability** | EDSS at 4FU | 77 | 4FU |
|  | EDSS worsening | 77 | 4FU |
| **Upper extremity function** | 9HPT dominant hand at 4 FU | 76 | 4FU |
|  | 9HPT dominant hand deterioration at 4FU | 76 | 4FU |
|  | 9HPT dominant hand baseline-to-follow-up-course | 149 | Baseline to 4FU |
|  | 9HT dominant hand time differences between 4FU and baseline | 76 | Baseline and 4FU |
|  | 9HPT non-dominant hand at 4 FU | 76 | 4FU |
|  | 9HPT non-dominant hand deterioration at 4FU | 76 | 4FU |
|  | 9HPT non-dominant hand baseline-to-follow-up-course | 149 | Baseline to 4FU |
|  | 9HT non-dominant hand time differences between 4FU and baseline | 76 | Baseline and 4FU |
| **Lower extremity function** | T25FW at 4 FU | 75 | 4FU |
|  | T25FW deterioration at 4FU | 75 | 4FU |
|  | T25FW baseline-to-follow-up-course | 149 | Baseline to 4FU |
|  | T25FW time differences between 4FU and baseline | 75 | Baseline and 4FU |
| **Cognitive function** | Cognitive impairment | 54 | 4FU and control group |
|  | PASAT3 at 4FU | 71 | 4FU |
|  | SDMT at 4FU | 72 | 4FU |
|  | PASAT3 baseline-to-follow-up-course | 149 | Baseline to 4FU |
|  | SDMT baseline-to-follow-up-course | 149 | Baseline to 4FU |
| **Quality of life** | HAQUAMS at 4FU | 69 | 4FU |
|  | SF36 at 4FU | 74 | 4FU |
| **Fatigue** | FSS at 4FU | 72 | 4FU |
|  | FSMC at 4FU | 72 | 4FU |
|  | FSMC severity at 4FU | 72 | 4FU |
| **Depressive symptoms** | BDI-II at 4FU | 69 | 4FU |
|  | BDI-II severity at 4FU | 69 | 4FU |

***Supplemental Table 1: Overview - research questions with sample sizes and timepoints of data assessment.*** *4FU, four-year follow-up; TTR, time to relapse; EDSS, Expanded disability status scale; 9HPT, Nine-Hole Peg Test; T25FW, Timed 25-foot walk test; PASAT3, Paced Auditory Serial Addition Test-3; SDMT, Symbol Digit Modalities Test; HAQUAMS, Hamburg Quality of Life Questionnaire in Multiple Sclerosis; SF36, Short Form 36; FSS, Fatigue Severity Scale; FSMC, Fatigue Scale for Motor and Cognitive Functions; BDI-II, Becks Depression Inventory-II.*

**Supplemental Table II: Baseline characteristics Table of all patients, who completed four-year follow-up**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **All patients** | **Female patients** | **Male patients** |
| Number of patients, n (%) | 85 (100) | 54 (63.53) | 31 (36.47) |
| Age at onset, years, mean (SD) | 33.18 (8.49) | 33.06 (8.52) | 33.39 (8.58) |
| BMI, mean (SD) | 24.47 (4.95) | 23.38 (4.29) | 26.49 (5.52) |
| Current smoker, n (%) | 20 (26.32) | 13 (27.66) | 7 (24.14) |
| Years of school education, mean (SD) | 12.26 (1.65) | 12.24 (1.85) | 12.30 (1.27) |
| Vitamin D level, nmol/l, mean (SD) | 52.57 (23.87) | 55.65 (25.08) | 48.18 (21.95) |
| Vitamin D deficiency (<50nmol/l), n (%) | 24 (52.17) | 14 (51.85) | 10 (52.63) |
| Received pharmacological treatment, n (%) | 21 (25.30) | 12 (22.64) | 9 (30.00) |
| EDSS baseline, median (IQR) | 1.50 (1.00) | 1.50 (1.00) | 1.50 (1.00) |
| mild (EDSS ≤2.5), n (%) | 79 (92.94) | 52 (96.30) | 27 (87.10) |
| moderate (EDSS 3.0–5.5), n (%) | 6 (7.06) | 2 (3.70) | 4 (12.90) |
| Timed 25-foot walk test, sec., mean (SD) | 4.24 (0.84) | 4.26 (0.77) | 4.19 (0.95) |
| Nine-hole peg test, dominant hand, sec., mean (SD) | 18.59 (2.49) | 18.16 (2.15) | 19.32 (2.89) |
| Nine-hole peg test, non- dominant hand, sec., mean (SD) | 19.42 (3.38) | 19.23 (3.83) | 19.76 (2.33) |
| BRB-N |  |  |  |
| SDMT, mean (SD) | 60.56 (10.90) | 60.65 (10.67) | 60.42 (11.44) |
| SRT-CLTR, mean (SD) | 56.90 (13.35) | 58.31 (12.51) | 54.58 (14.53) |
| SRT-LTS, mean (SD) | 60.01 (9.79) | 61.20 (9.04) | 58.06 (10.79) |
| SRT-DR, mean (SD) | 11.30 (1.41) | 11.41 (1.19) | 11.13 (1.73) |
| SPAT, mean (SD) | 23.90 (4.27) | 23.16 (4.69) | 25.13 (3.19) |
| SPAT-DR, mean (SD) | 8.83 (1.70) | 8.65 (1.84) | 9.13 (1.41) |
| WLG, mean (SD) | 27.24 (6.03) | 28.75 (5.76) | 24.77 (5.71) |
| PASAT3, mean (SD) | 48.96 (9.18) | 48.89 (10.27) | 49.10 (7.10) |
| MRI parameters |  |  |  |
| T2 hyperintense lesion count, median (IQR) | 13.00 (19.00) | 10.00 (16.00) | 17.00 (22.50) |
| Volume of T2 hyperintense lesions, ml, mean (SD) | 2.09 (3.45) | 2.03 (3.37) | 2.21 (3.64) |

***Supplemental Table II: Baseline characteristics Table of all patients, who completed 4-year follow-up.*** *N,number of patients; SD, standard deviation; IQR, interquartile range; BMI, Body-Mass-Index; EDSS, Expanded Disability Status Scale; BRB-N, Brief Repeatable Battery of Neuropsychological Tests; SDMT, Symbol Digit Modalities Test; SRT-CLTR, Selective Reminding Test-Consistent Long-Term Retrieval; SRT-LTS, Selective Reminding Test-Long Term Storage; SRT-DR, Selective Reminding Test-Delayed recall; SPAT, 10/36 Spatial Recall Test; SPAT-DR, 10/36 Spatial Recall Test-Delayed recall; WLG, Word List Generation test; PASAT3, Paced Auditory Serial Addition Test-3; MRI, Magnetic resonance imaging.*

The proportion of missing data was less than 10% in all parameters in Table 1, except for information on BMI (20.0%), smoking status (10.6%), years in school (12.9%) and vitamin D level and deficiency (45.9%).

**Supplemental Table III: Baseline characteristics Table of all patients, who did not complete four-year follow-up**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **All patients** | **Female patients** | **Male patients** |
| Number of patients, n (%) | 64 (100) | 43 (67.19) | 21 (32.81) |
| Age at onset, years, mean (SD) | 31.52 (7.88) | 31.53 (7.77) | 31.48 (8.28) |
| BMI, mean (SD) | 24.21 (4.55) | 23.72 (4.62) | 25.29 (4.34) |
| Current smoker, n (%) | 6 (26.09) | 4 (26.67) | 2 (25.00) |
| Years of school education, mean (SD) | 12.65 (1.40) | 12.62 (1.41) | 12.71 (1.50) |
| Vitamin D level, nmol/l, mean (SD) | 45.75 (19.35) | 45.40 (18.33) | 47.38 (25.99) |
| Vitamin D deficiency (<50nmol/l), n (%) | 15 (53.57) | 13 (56.52) | 2 (40.00) |
| Received pharmacological treatment, n (%) | 27 (45.76) | 18 (45.00) | 9 (33.33) |
| EDSS baseline, median (IQR) | 1.50 (1.00) | 1.50 (0.50) | 1.50 (1.50) |
| mild (EDSS ≤2.5), n (%) | 58 (90.62) | 41 (95.35) | 17 (80.95) |
| moderate (EDSS 3.0–5.5), n (%) | 6 (9.38) | 2 (4.65) | 4 (19.05) |
| Timed 25-foot walk test, sec., mean (SD) | 4.09 (0.63) | 4.14 (0.68) | 3.99 (0.52) |
| Nine-hole peg test, dominant hand, sec., mean (SD) | 18.64 (2.48) | 18.17 (2.32) | 19.60 (2.57) |
| Nine-hole peg test, non- dominant hand, sec., mean (SD) | 19.60 (2.62) | 19.60 (2.82) | 19.58 (2.25) |
| BRB-N |  |  |  |
| SDMT, mean (SD) | 59.30 (10.59) | 58.69 (9.00) | 60.52 (13.40) |
| SRT-CLTR, mean (SD) | 56.66 (13.13) | 58.80 (11.13) | 52.66 (13.13) |
| SRT-LTS, mean (SD) | 60.21 (9.38) | 62.05 (8.10) | 56.45 (10.83) |
| SRT-DR, mean (SD) | 11.42 (1.03) | 11.66 (0.79) | 10.95 (1.28) |
| SPAT, mean (SD) | 23.15 (4.49) | 22.77 (4.42) | 23.86 (4.65) |
| SPAT-DR, mean (SD) | 8.68 (1.53) | 8.63 (1.56) | 8.76 (1.51) |
| WLG, mean (SD) | 27.06 (5.92) | 28.00 (6.31) | 25.10 (4.54) |
| PASAT3, mean (SD) | 49.52 (8.93) | 48.43 (8.85) | 51.80 (8.89) |
| MRI parameters |  |  |  |
| T2 hyperintense lesion count, median (IQR) | 13.00 (24.25) | 10.50 (19.75) | 16.00 (27.50) |
| Volume of T2 hyperintense lesions, ml, mean (SD) | 2.17 (2.54) | 1.79 (2.17) | 2.96 (3.09) |

***Supplemental Table III: Baseline characteristics Table of all patients, who did not complete 4-year follow-up.*** *N, number of patients; SD, standard deviation; IQR, interquartile range; BMI, Body-Mass-Index; EDSS, Expanded Disability Status Scale; BRB-N, Brief Repeatable Battery of Neuropsychological Tests; SDMT, Symbol Digit Modalities Test; SRT-CLTR, Selective Reminding Test-Consistent Long-Term Retrieval; SRT-LTS, Selective Reminding Test-Long Term Storage; SRT-DR, Selective Reminding Test-Delayed recall; SPAT, 10/36 Spatial Recall Test; SPAT-DR, 10/36 Spatial Recall Test-Delayed recall; WLG, Word List Generation test; PASAT3, Paced Auditory Serial Addition Test-3; MRI, Magnetic resonance imaging.*

The proportion of missing data was less than 10% in all parameters in Table 1, except for information on BMI (14.1%), smoking status (64.1%), years in school (64.1%) and vitamin D level and deficiency (56.3%).

**Supplemental Table IV: Results of SF36 subscales**

|  |  |  |  |
| --- | --- | --- | --- |
| **SF36 Subscale** | **β effect size (95%CI)** | **Female**  **mean (SD)** | **Male**  **mean (SD)** |
| Physical function | -3.89 (-8.34-0.57) | 99.15 (1.94) | 95.26 (11.96) |
| Pain | -2.76 (-11.52-6.07) | 91.26 (15.20) | 88.54 (22.67) |
| Role limitations due to physical health | -2.54 (-15.14-10.05) | 93.33 (19.62) | 90.79 (23.88) |
| General health perceptions | -1.74 (-11.46-7.99) | 70.63 (19.73) | 68.89 (21.35) |
| Vitality | -1.71 (-11.77-8.34) | 62.61 (20.84) | 60.89 (21.39) |
| Social functioning | 1.24 (-8.89-11.38) | 88.04 (22.51) | 89.29 (18.85) |
| Role limitations due to personal or emotional problems | 1.76 (-10.80- 14.32) | 85.14 (25.39) | 86.90 (27.72) |
| Emotional well-being: | 2.32 (-5.32-9.96) | 77.39 (16.95) | 79.71 (14.23) |

***Supplemental Table IV: Results of SF36 subscales****. SF36, Short From 36; 95%CI, 95% confidence interval; SD, standard deviation.*

**Supplemental Figure I: Linear effect sizes of clinical outcomes - SF36 after 4 years.**

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**Supplemental Figure I: Linear effect sizes of clinical outcomes - SF36 after 4 years.** Each line represents one SF36 subscale with β effect size and 95%CI. Effect sizes greater than 0 indicate that males scored higher in the respective subtest. (Min, minimal achievable score; max, maximal achievable score).

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