**SUPPLEMENTAL MATERIALS**

**Supplemental Figure 1.** Funnel plots for all analyses



**Supplemental Table 1.** PRISMA checklist

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | |  |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3-4 |
| **METHODS** | | |  |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 4 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4-5 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supplemental  Table 2 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 6 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | 6-7 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6-7 |
| **RESULTS** | | |  |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 7,  Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 7,  Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 7,  Table 1, Supplemental Table 4 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Figures 2-5 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 8-9, Figures 2-5 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 8-9, Supplemental Figure 1 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 8-9 |
| **DISCUSSION** | | |  |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 10-11 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 11 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 11 |
| **FUNDING** | | |  |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 12 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

**Supplemental Table 2.** Ovid Search Strategy

1.  multiple sclerosis.mp.

2.  exp multiple sclerosis/

3.  1 or 2

4.  ((cognit$ or memory or mental or brain or attention or reasoning or neurocognit$ or neuropsycholog$ or speed) adj3 (retraining or training$ or exercis$ or stimulat$ or enhanc$ or rehabilitat$ or remediat$ or restructur$ or activit$ or interven$)).mp.

5.  (video gam$ or videogam$ or wii or computer gam$ or virtual reality).mp.

6.  4 or 5

7.  3 and 6

**Supplemental Table 3.** Categorization of outcome measures to individual domains

|  |  |  |
| --- | --- | --- |
| **Cognitive** |  | **Psychosocial** |
| *Attention/speed* | *Executive functions* | *Depression* |
| Conners' Continuous Performance Test-II | Computer-aided card-sorting procedure (modified form) | Beck Depression Inventory |
| Sustained attention (Schuhfried Daueraufmerksamkeit) | Controlled Oral Word Association Test | Hospital Anxiety and Depression Scale (Depression) |
| Delis-Kaplan Executive Function System: Trail 2/3 | Delis-Kaplan Executive Function System: Sorting | Montgomery–Åsberg Depression Rating Scale |
| Trail Making Test Part A | Trail Making Test Part B | Center for Epidemiologic Studies Depression Scale |
| Pattern Comparison |  |  |
| Letter Comparison | Phonemic Fluency | *Quality of life* |
| Paced Auditory Serial Addition Task | Semantic Fluency | EuroQOL |
| Testbatterie zur Aufmerksamkeitsprüfung | Hamburg Wechsler Intelligence Test: Mosaic Test | Functional Assessment of MS |
| Symbol Digit Modalities Test | MUSIC: Interferences | 36-Item Short Form Survey |
| Test of Everyday Attention | MUSIC: Verbal Fluency | MSQoL-54 |
|  | Raven's Advanced Progressive Matrices |  |
| *Verbal memory* | Stroop | *Subjective cognitive assessment / meta-cognition* |
| Auditory Verbal Learning Test | Wisconsin Card Sorting Test | Multifactorial Memory Questionnaire |
| Buschke Selective Reminding Test | Word List Generation | MS Neuropsychological Questionnaire |
| California Verbal Learning Test |  | Patient Reported Outcomes Measurement Information System (PROMIS) Cognitive Ability |
| Multiple Sklerose Inventarium Cognition (MUSIC):  Verbal memory and retrieval |  |  |
| Verbal Learning Test |  | *Disease management / Self-efficacy* |
|  | **Functional** | Patient Activation Measure (PAM-13) |
| *Visuospatial memory* | *ADL* | Multiple sclerosis Self-Efficacy Scale: Control |
| 10/36 Spatial Recall Test | Barthel Index | Unidimensional Self-Eficacy scale for MS |
| Brief Visuospatial Memory Test | Everyday Problems Test-Revised (EPT-R) |  |
| Non-verbal learning test | Timed Instrumental Activities of Daily Living |  |
|  |  |  |
| *Working memory* | *Disability* |  |
| Corsi Block | Expanded Disability Status Scale |  |
| Digit Span Backward | Rivermead Mobility Index |  |
| Letter-Number Sequencing |  |  |
|  | **Fatigue** |  |
| *Visuospatial skills* | Fatigue Severity Scale |  |
| Judgement of Line Orientation | Fatigue Scale for Motor and Cognitive functions |  |
|  | Modified Fatigue Impact Scale |  |
|  |  |  |

**Supplemental Table 4.** Risk of Bias within studies

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Sequence**  **generation** | **Allocation**  **concealment** | **Participant and blinding** | **Therapist**  **blinding** | **Assessor**  **Blinding** | **Incomplete**  **outcome data** | **Selective**  **outcome**  **reporting** | **Other sources of bias** | **Summary** |
| **Amato 20141** | Low | Unclear | Unclear | High | Low | High | High | Unclear | **High** |
| **Campbell 20162** | Low | Unclear | High | High | High | High | Unclear | Unclear | **High** |
| **Cerasa 20133** | Low | Low | Unclear | Unclear | Low | High | Unclear | Unclear | **High** |
| **Charvet 20154** | Unclear | Low | Unclear | High | Low | Low | Unclear | Unclear | **Low** |
| **Charvet 20175** | Low | Low | Unclear | High | Low | Low | Unclear | Unclear | **Low** |
| **Chiaravalloti 20186** | Low | Low | High | High | Low | Low | High | Unclear | **Low** |
| **De Giglio 20157** | Low | Low | High | High | Low | High | High | Unclear | **High** |
| **Grasso 20178** | Low | Unclear | High | Unclear | Low | Unclear | Unclear | Unclear | **High** |
| **Hancock 20159** | Low | Unclear | Unclear | Unclear | Low | High | Unclear | Unclear | **High** |
| **Hubacher 201510** | Unclear | High | High | High | High | Low | High | High | **High** |
| **Janssen 201511** | Unclear | Unclear | High | High | Low | High | Unclear | Unclear | **High** |
| **Mattioli 201012** | Unclear | Low | Unclear | High | Low | Low | High | Unclear | **Low** |
| **Messinis 201713** | Low | Low | High | High | High | Low | Unclear | Unclear | **High** |
| **Pedulla 201614** | Unclear | Low | Unclear | High | Unclear | High | Unclear | Unclear | **High** |
| **Perez-Martin 201715** | Unclear | Unclear | High | High | Low | Low | Unclear | Unclear | **Low** |
| **Pusswald 201416** | Unclear | Unclear | High | High | High | Low | High | Unclear | **High** |
| **Solari 200417** | Low | Low | Unclear | High | Low | High | Unclear | High | **High** |
| **Stuifbergen 201218** | Unclear | Low | High | High | Low | Unclear | Unclear | Unclear | **High** |
| **Stuifbergen 201819** | Unclear | Low | High | High | Low | Unclear | Low | Low | **High** |
| **Tessar 200520** | Unclear | Unclear | High | High | High | High | High | Unclear | **High** |

**Supplemental Table 5.** Meta-analyses of psychosocial and functional sub-domains

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Domain** | ***k*** | **Hedges’ *g* (95% CI)** | **τ2** | ***I*2** |
| *Psychosocial functioning* |  |  |  |  |
| Depression | 7 | 0.21 (-0.05 – 0.46) | 0.02 | 17.2% |
| Quality of life | 4 | 0.27 (-0.03 – 0.57) | 0 | 0% |
| Subjective cognition | 4 | 0.24 (-0.03 – 0.51) | 0.02 | 26.3% |
| Anxiety | 3 | 0.38 (-0.46 – 1.21) | 0.42 | 77.8% |
|  |  |  |  |  |
| *Function* |  |  |  |  |
| Disease management | 3 | 0.05 (-0.19 – 0.29) | 0 | 0% |
| Activities of daily living | 3 | 0.10 (-0.22 – 0.42) | 0.02 | 14.5% |
| Disability | 1 | 0.02 (-0.64 – 0.68) | 0 | 0% |

**References**

1. Amato MP, Goretti B, Viterbo RG, et al. Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial. *Mult Scler.* 2014;20(1):91-98.

2. Campbell J, Langdon D, Cercignani M, Rashid W. A Randomised Controlled Trial of Efficacy of Cognitive Rehabilitation in Multiple Sclerosis: A Cognitive, Behavioural, and MRI Study. *Neural Plast.* 2016;2016:4292585.

3. Cerasa A, Gioia MC, Valentino P, et al. Computer-assisted cognitive rehabilitation of attention deficits for multiple sclerosis: a randomized trial with fMRI correlates. *Neurorehabil Neural Repair.* 2013;27(4):284-295.

4. Charvet LE, Shaw MT, Haider L, Melville P, Krupp LB. Remotely-delivered cognitive remediation in multiple sclerosis (MS): protocol and results from a pilot study. *Mult Scler J Exp Transl Clin.* 2015;1:2055217315609629.

5. Charvet LE, Yang J, Shaw MT, et al. Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial. *PLoS One.* 2017;12(5):e0177177.

6. Chiaravalloti ND, Goverover Y, Costa SL, DeLuca J. A Pilot Study Examining Speed of Processing Training (SPT) to Improve Processing Speed in Persons With Multiple Sclerosis. *Frontiers in neurology.* 2018;9:685.

7. De Giglio L, De Luca F, Prosperini L, et al. A low-cost cognitive rehabilitation with a commercial video game improves sustained attention and executive functions in multiple sclerosis: a pilot study. *Neurorehabil Neural Repair.* 2015;29(5):453-461.

8. Grasso MG, Broccoli M, Casillo P, et al. Evaluation of the Impact of Cognitive Training on Quality of Life in Patients with Multiple Sclerosis. *Eur Neurol.* 2017;78(1-2):111-117.

9. Hancock LM, Bruce JM, Bruce AS, Lynch SG. Processing speed and working memory training in multiple sclerosis: a double-blind randomized controlled pilot study. *J Clin Exp Neuropsychol.* 2015;37(2):113-127.

10. Hubacher M, Kappos L, Weier K, Stocklin M, Opwis K, Penner IK. Case-Based fMRI Analysis after Cognitive Rehabilitation in MS: A Novel Approach. *Frontiers in neurology.* 2015;6:78.

11. Janssen A, Boster A, Lee H, Patterson B, Prakash RS. The effects of video-game training on broad cognitive transfer in multiple sclerosis: A pilot randomized controlled trial. *J Clin Exp Neuropsychol.* 2015;37(3):285-302.

12. Mattioli F, Stampatori C, Zanotti D, Parrinello G, Capra R. Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis. *J Neurol Sci.* 2010;288(1-2):101-105.

13. Messinis L, Nasios G, Kosmidis MH, et al. Efficacy of a Computer-Assisted Cognitive Rehabilitation Intervention in Relapsing-Remitting Multiple Sclerosis Patients: A Multicenter Randomized Controlled Trial. *Behav Neurol.* 2017;2017:5919841.

14. Pedulla L, Brichetto G, Tacchino A, et al. Adaptive vs. non-adaptive cognitive training by means of a personalized App: a randomized trial in people with multiple sclerosis. *J Neuroeng Rehabil.* 2016;13(1):88.

15. Perez-Martin MY, Gonzalez-Platas M, Eguia-Del Rio P, Croissier-Elias C, Jimenez Sosa A. Efficacy of a short cognitive training program in patients with multiple sclerosis. *Neuropsychiatr Dis Treat.* 2017;13:245-252.

16. Pusswald G, Mildner C, Zebenholzer K, Auff E, Lehrner J. A neuropsychological rehabilitation program for patients with Multiple Sclerosis based on the model of the ICF. *NeuroRehabilitation.* 2014;35(3):519-527.

17. Solari A, Motta A, Mendozzi L, et al. Computer-aided retraining of memory and attention in people with multiple sclerosis: a randomized, double-blind controlled trial.[Erratum appears in J Neurol Sci. 2004 Sep 15;224(1-2):113]. *J Neurol Sci.* 2004;222(1-2):99-104.

18. Stuifbergen AK, Becker H, Perez F, Morison J, Kullberg V, Todd A. A randomized controlled trial of a cognitive rehabilitation intervention for persons with multiple sclerosis. *Clin Rehabil.* 2012;26(10):882-893.

19. Stuifbergen AK, Becker H, Perez F, et al. Computer-assisted cognitive rehabilitation in persons with multiple sclerosis: Results of a multi-site randomized controlled trial with six month follow-up. *Disability and health journal.* 2018;11(3):427-434.

20. Tesar N, Bandion K, Baumhackl U. Efficacy of a neuropsychological training programme for patients with multiple sclerosis -- a randomised controlled trial. *Wien Klin Wochenschr.* 2005;117(21-22):747-754.