# APPENDIX A. SEARCH STRATEGIES

This appendix documents the exact search strings for all searched electronic databases. We designed a search strategy for each key question in order to maximize relevance and retrieval success.

## SEARCH METHODOLOGY KQ1

**DATABASE SEARCHED & TIME PERIOD COVERED:**
PubMed – ~1946-2/27/2015
**LANGUAGE:**
English
**SEARCH STRATEGY #1 (Study Design Filter):**
multiple sclerosis[tiab] OR multiple sclerosis[majr]
AND
progression[tiab] OR progressive[tiab] OR progressing[tiab] OR mortality[tiab] OR disease course[tiab] OR disability[tiab]
AND
"cohort studies"[mh] OR "follow-up studies"[mh] OR prognos*[tiab] OR predict*[tiab] OR multivariate[tiab]
NOT
(animal OR animals) NOT (human OR humans)

**SEARCH STRATEGY #2 (Risk Factor Filter):**
multiple sclerosis[tiab] OR multiple sclerosis[majr]
AND
progression[tiab] OR progressive[tiab] OR progressing[tiab] OR mortality[tiab] OR disease course[tiab] OR disability[tiab]
AND
geographic[tiab] OR sun exposure[tiab] OR vitamin D[tiab] OR fatty acid[tiab] OR diet[tiab] OR dietary[tiab] OR nutrition*[tiab] OR obesity[tiab] OR smoking[tiab] OR tobacco[tiab] OR alcohol[tiab] OR exercise[tiab] OR physical activity[tiab] OR stress[tiab] OR anesthesia[tiab] OR radiation therapy[tiab] OR oral contraception[tiab] OR fertility treatment[tiab] OR pregnan*[tiab] OR delivery[tiab] OR breastfeeding[tiab] OR salt intake[tiab] OR milk[tiab] OR water[tiab] OR trace elements[tiab] OR trauma[tiab] OR traumatic[tiab] OR Epstein–Barr virus[tiab]
NOT
(animal OR animals) NOT (human OR humans)

**DATABASE SEARCHED & TIME PERIOD COVERED:**
Web of Science– Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH - 1980-2/27/2015
**LANGUAGE:**
English
**SEARCH STRATEGY #1:**
TS = (multiple sclerosis)
AND
TS = (progression OR progressive OR progressing)
AND
TS = (cohort OR prognos*OR predict* OR multivariate)

**SEARCH STRATEGY #2:**
TS = (multiple sclerosis)

AND
TS = (progression OR progressive OR progressing)
AND
TS = (geographic OR sun OR sunlight OR vitamin D OR fatty acid OR diet OR dietary OR nutrition* OR obesity OR obese OR smoking OR tobacco OR alcohol OR exercise OR physical activity OR stress* OR anesthesia OR radiation therapy OR oral contracepti* OR fertility treatment OR pregnan* OR breastfeed* OR salt OR milk OR water OR trace elements OR trauma OR traumatic OR Epstein–Barr OR "Epstein barr")

**DATABASE SEARCHED & TIME PERIOD COVERED:**
SCOPUS – ~1800's-3/2/2015
**LANGUAGE:**
English
**SEARCH STRATEGY #1:**
TITLE-ABS-KEY("multiple sclerosis")
AND
TITLE-ABS-KEY(progression OR progressive OR progressing)
AND
TITLE-ABS-KEY(cohort OR prognos*OR predict* OR multivariate)

**SEARCH STRATEGY #2:**
TITLE-ABS-KEY ( "multiple sclerosis")
AND
TITLE-ABS-KEY ( progression OR progressive OR progressing )
AND
vitamin d OR fatty acid OR diet OR dietary OR nutrition* OR obesity OR obese OR smoking OR tobacco OR alcohol ) OR ( geographic OR sun OR sunlight OR exercise OR physical activity OR stress* OR anesthesia OR radiation therapy OR oral contracepti* ) OR ( fertility treatment OR pregnan* OR breastfeed* OR salt OR milk OR water OR trace elements OR trauma OR traumatic OR epstein--barr OR "Epstein barr"

**DATABASE SEARCHED & TIME PERIOD COVERED:**
GreenFILE - ~1970's- 3/2/2015
**SEARCH STRATEGY:**
"multiple sclerosis"

## SEARCH METHODOLOGY KQ2

**DATABASE SEARCHED & TIME PERIOD COVERED:**
PubMed – Earliest-3/16/2015
**LANGUAGE:**
English
**SEARCH STRATEGY:**
multiple sclerosis
AND
United States Department of Veterans Affairs[mh] OR Veterans Health[mh] OR Hospitals, Veterans[mh] OR Veterans Disability Claims[mh] OR Veterans[mh] OR military personnel[mh] OR military medicine[mh] OR veteran* or military or army or navy or naval or air force or marines or coast guard or

national guard or soldier* or guardsmen or reservist* or troops or infantry* or armed forces or armed service* or war or wars or war-related or combat* or battle* or service-member*

**DATABASE SEARCHED & TIME PERIOD COVERED:**
Embase – Earliest-3/23/2015
**LANGUAGE:**
English
**SEARCH STRATEGY:**
'multiple sclerosis'
AND
military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members' OR 'veteran'/exp OR 'veteran' OR veteran*:ti OR 'veterans health'/de OR 'veterans health'

**DATABASE SEARCHED & TIME PERIOD COVERED:**
Web of Science Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH– 1/1/1980-3/23/2015
**LANGUAGE:**
English
**SEARCH STRATEGY:**
TOPIC: ("multiple sclerosis")
AND
TOPIC: (veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members')

**DATABASE SEARCHED & TIME PERIOD COVERED:**
SCOPUS– Earliest-3/23/2015
**LANGUAGE:**
English
**SEARCH STRATEGY:**
TITLE-ABS-KEY("multiple sclerosis")
AND
ALL(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle OR 'service member' OR 'service members' )

**DATABASE SEARCHED & TIME PERIOD COVERED:**
AMED– Earliest-3/23/2015
**LANGUAGE:**
English
**SEARCH STRATEGY:**
ti("multiple sclerosis") OR su("multiple sclerosis")
AND
ab(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR

'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members') OR ti(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members') OR su(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members')

**DATABASE SEARCHED & TIME PERIOD COVERED:**
GreenFILE– Earliest-3/23/2015
**LANGUAGE:**
English
**SEARCH STRATEGY:**
multiple sclerosis
**NUMBER OF RESULTS: 49**

**DATABASE SEARCHED & TIME PERIOD COVERED:**
Proquest Military Collection – Earliest-3/23/2015
**LANGUAGE:**
English
**SEARCH STRATEGY:**
(ti("multiple sclerosis") OR ab("multiple sclerosis") OR su("multiple sclerosis"))
AND
(ab(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members') OR ti(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members') OR su(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members'))

**DATABASE SEARCHED & TIME PERIOD COVERED:**
DTIC Technical Reports Collections – Earliest-3/17/2015
**SEARCH STRATEGY:**
exact phrase: Multiple sclerosis
AND
Veterans

## SEARCH METHODOLOGY KQ3

This section documents the exact search strings used to identify studies relevant for KQ3.

**DATABASE SEARCHED & TIME PERIOD COVERED:**
PubMed – Earliest-1/13/2015
**FILTERS:**
English, Randomized Controlled Trial
**SEARCH STRATEGY:**
"multiple sclerosis"

**DATABASE SEARCHED & TIME PERIOD COVERED:**
AMED – Earliest-3/3/2015
**SEARCH STRATEGY:**
"multiple sclerosis" AND interven* AND (random* OR rct*)

**DATABASE SEARCHED & TIME PERIOD COVERED:**
Web of Science – Earliest-3/3/2015
**SEARCH STRATEGY:**
TS = (multiple sclerosis)
AND
TS = (geographic OR sun OR sunlight OR vitamin D OR fatty acid OR diet OR dietary OR nutrition* OR obesity OR obese OR smoking OR tobacco OR alcohol OR exercise OR physical activity OR stress* OR anesthesia OR radiation therapy OR oral contracepti* OR fertility treatment OR pregnan* OR breastfeed* OR salt OR milk OR water OR trace elements OR trauma OR traumatic OR Epstein–Barr OR "Epstein barr"))
AND
ts = (intervention* OR intervene*)
AND
LANGUAGE: (English)

# APPENDIX B. STUDY SELECTION AND LIST OF EXCLUDED STUDIES

The search yield, title and abstract screening results; full text decisions, and the data extraction are documented in electronic databases which can be obtained from the authors, in compliance with standard data sharing requirements.

This appendix lists the citation of publications obtained as full text but not meeting inclusion criteria together with the reason for excluding the publication.

## EXCLUDE: OUTCOME

Excluded publications not reporting on MS progression:


1. Acheson ED, Bachrach CA. The distribution of multiple sclerosis in U. S. veterans by birthplace. *American Journal of Hygiene.* Jul 1960;72:88-99.
2. Ackerman KD, Stover A, Heyman R, et al. Relationship of cardiovascular reactivity, stressful life events, and multiple sclerosis disease activity. *Brain Behav. Immun.* Jun 2003;17(3):141-151.
3. Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Oct 2001;7(5):340-344.
4. Ayatollahi P, Nafissi S, Eshraghian MR, Kaviani H, Tarazi A. Impact of depression and disability on quality of life in Iranian patients with multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Mar 2007;13(2):275-277.
5. Bansi J, Bloch W, Gamper U, Kesselring J. Training in MS: influence of two different endurance training protocols (aquatic versus overland) on cytokine and neurotrophin concentrations during three week randomized controlled trial. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2013;19(5):613-621.
6. Barth SK, Kang HK, Bullman TA, Wallin MT. Neurological mortality among U.S. veterans of the Persian Gulf War: 13-year follow-up. *American Journal of Industrial Medicine.* Sep 2009;52(9):663-670.
7. Basak T, Unver V, Demirkaya S. Activities of Daily Living and Self-Care Agency in Patients with Multiple Sclerosis for the First 10 Years. *Rehabilitation Nursing: The Official Journal of the Association of Rehabilitation Nurses.* Mar 25 2014.
8. Baumstarck K, Pelletier J, Boucekine M, Auquier P. Predictors of quality of life in patients with relapsing-remitting multiple sclerosis: A 2-year longitudinal study. *Rev Neurol (Paris).* Feb 2015;171(2):173-180.
9. Bayraktar D, Guclu-Gunduz A, Yazici G, et al. Effects of Ai-Chi on balance, functional mobility, strength and fatigue in patients with multiple sclerosis: a pilot study. *NeuroRehabilitation.* 2013;33(3):431-437.
10. Bee YS, Lin MC, Wang CC, Sheu SJ. Optic neuritis: clinical analysis of 27 cases. *The Kaohsiung Journal of Medical Sciences.* Mar 2003;19(3):105-112.
11. Beebe GW, Kurtzke JF. Herpes zoster and multiple sclerosis. *British Medical Journal.* Nov 1 1969;4(5678):303.
12. Beebe GW, Kurtzke JF, Kurland LT, Auth TL, Nagler B. Studies on the natural history of multiple sclerosis. 3. Epidemiologic analysis of the army experience in World War II. *Neurology.* Jan 1967;17(1):1-17.
13. Beer S, Aschbacher B, Manoglou D, Gamper E, Kool J, Kesselring J. Robot-assisted gait training in multiple sclerosis: a pilot randomized trial. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Mar 2008;14(2):231-236.
14. Beier M, D'Orio V, Spat J, Shuman M, Foley FW. Alcohol and substance use in multiple sclerosis. *Journal of the Neurological Sciences.* Mar 15 2014;338(1-2):122-127.
15. Bobowick AR, Kurtzke JF, Brody JA, Hrubec Z, Gillespie M. Twin study of multiple sclerosis: an epidemiologic inquiry. *Neurology.* Oct 1978;28(10):978-987.
16. Bombardier CH, Cunniffe M, Wadhwani R, Gibbons LE, Blake KD, Kraft GH. The efficacy of telephone counseling for health promotion in people with multiple sclerosis: a randomized controlled trial. *Archives of Physical Medicine and Rehabilitation.* Oct 2008;89(10):1849-1856.
17. Bombardier CH, Ehde DM, Gibbons LE, et al. Telephone-based physical activity counseling for major

depression in people with multiple sclerosis. *Journal of Consulting and Clinical Psychology*. Feb 2013;81(1):89-99.
18. Briken S, Gold SM, Patra S, et al. Effects of exercise on fitness and cognition in progressive MS: a randomized, controlled pilot trial. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Mar 2014;20(3):382-390.
19. Broekmans T, Roelants M, Alders G, Feys P, Thijs H, Eijnde BO. Exploring the effects of a 20-week whole-body vibration training programme on leg muscle performance and function in persons with multiple sclerosis. *J Rehabil Med.* Oct 2010;42(9):866-872.
20. Broekmans T, Roelants M, Feys P, et al. Effects of long-term resistance training and simultaneous electro-stimulation on muscle strength and functional mobility in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2011;17(4):468-477.
21. Brown JS, Jr. Correlation of mollicutes and their viruses with multiple sclerosis and other demyelinating diseases. *Medical Hypotheses.* Feb 2003;60(2):298-303.
22. Buljevac D, Hop WC, Reedeker W, et al. Self reported stressful life events and exacerbations in multiple sclerosis: prospective study. *BMJ.* Sep 20 2003;327(7416):646.
23. Burschka JM, Keune PM, Oy UH, Oschmann P, Kuhn P. Mindfulness-based interventions in multiple sclerosis: beneficial effects of Tai Chi on balance, coordination, fatigue and depression. *BMC Neurol.* 2014;14:165.
24. Cakt BD, Nacir B, Genc H, et al. Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists.* Jun 2010;89(6):446-457.
25. Carter A, Daley A, Humphreys L, et al. Pragmatic intervention for increasing self-directed exercise behaviour and improving important health outcomes in people with multiple sclerosis: a randomised controlled trial. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jan 13 2014;20(8):1112-1122.
26. Carvalho AT, Veiga A, Morgado J, et al. Multiple sclerosis and motherhood choice: an observational study in Portuguese women patients. *Revista de Neurologia.* Dec 16 2014;59(12):537-542.
27. Castro-Sanchez AM, Mataran-Penarrocha GA, Lara-Palomo I, Saavedra-Hernandez M, Arroyo-Morales M, Moreno-Lorenzo C. Hydrotherapy for the treatment of pain in people with multiple sclerosis: a randomized controlled trial. *Evidence-based Complementary and Alternative Medicine: eCAM.* 2012;2012:473963.
28. Cattaneo D, Jonsdottir J, Zocchi M, Regola A. Effects of balance exercises on people with multiple sclerosis: a pilot study. *Clin Rehabil.* Sep 2007;21(9):771-781.
29. Chataway J, Schuerer N, Alsanousi A, et al. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. *Lancet.* Jun 28 2014;383(9936):2213-2221.
30. Chruzander C, Johansson S, Gottberg K, et al. A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm, Sweden: changes in disability and the value of different factors in predicting disability and mortality. *Journal of the Neurological Sciences.* Sep 15 2013;332(1-2):121-127.
31. Cioncoloni D, Innocenti I, Bartalini S, et al. Individual factors enhance poor health-related quality of life outcome in multiple sclerosis patients. Significance of predictive determinants. *Journal of the Neurological Sciences.* Oct 15 2014;345(1-2):213-219.
32. Claerbout M, Gebara B, Ilsbroukx S, et al. Effects of 3 weeks' whole body vibration training on muscle strength and functional mobility in hospitalized persons with multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2012;18(4):498-505.
33. Collett J, Dawes H, Meaney A, et al. Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities. *Multiple Sclerosis (Houndmills, Basingstoke, England).* May 2011;17(5):594-603.
34. Coote S, Hughes L, Rainsford G, Minogue C, Donnelly A. Pilot randomized trial of progressive resistance exercise augmented by neuromuscular electrical stimulation for people with multiple sclerosis who use walking AIDS. *Archives of Physical Medicine and Rehabilitation.* Feb 2015;96(2):197-204.
35. Dalgas U, Stenager E, Jakobsen J, et al. Fatigue, mood and quality of life improve in MS patients after progressive resistance training. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2010;16(4):480-490.
36. Dettmers C, Sulzmann M, Ruchay-Plossl A, Gutler R, Vieten M. Endurance exercise improves walking distance in MS patients with fatigue. *Acta Neurologica Scandinavica.* Oct 2009;120(4):251-257.
37. D'Hooghe M B, Feys P, Deltour S, et al. Impact of a 5-day expedition to machu picchu on persons with multiple sclerosis. *Multiple Sclerosis International.* 2014;2014:761210.
38. Dlugonski D, Motl RW, Mohr DC, Sandroff BM. Internet-delivered behavioral intervention to increase

physical activity in persons with multiple sclerosis: sustainability and secondary outcomes. *Psychology, Health & Medicine.* 2012;17(6):636-651.
39. Dodd KJ, Taylor NF, Shields N, Prasad D, McDonald E, Gillon A. Progressive resistance training did not improve walking but can improve muscle performance, quality of life and fatigue in adults with multiple sclerosis: a randomized controlled trial. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Nov 2011;17(11):1362-1374.
40. Eftekhari E, Mostahfezian M, Etemadifar M, Zafari A. Resistance training and vibration improve muscle strength and functional capacity in female patients with multiple sclerosis. *Asian Journal of Sports Medicine.* Dec 2012;3(4):279-284.
41. Ennis M, Thain J, Boggild M, Baker GA, Young CA. A randomized controlled trial of a health promotion education programme for people with multiple sclerosis. *Clin Rehabil.* Sep 2006;20(9):783-792.
42. Fernandez-Jimenez E, Arnett PA. Impact of neurological impairment, depression, cognitive function and coping on quality of life of people with multiple sclerosis: A relative importance analysis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Dec 22 2014.
43. Fryze W, Mirowska-Guzel D, Wiszniewska M, Darda-Ledzion L, Czlonkowska A, Czlonkowska A. Alternative methods of treatment used by multiple sclerosis patients in Poland. *Neurologia i Neurochirurgia Polska.* 2006;40(5):386-390.
44. Garrett M, Hogan N, Larkin A, Saunders J, Jakeman P, Coote S. Exercise in the community for people with multiple sclerosis - a follow-up of people with minimal gait impairment. *Mult. Scler. J.* May 2013;19(6):790-798.
45. Glad SB, Aarseth JH, Nyland H, Riise T, Myhr KM. Benign multiple sclerosis: a need for a consensus. *Acta Neurologica Scandinavica. Supplementum.* 2010(190):44-50.
46. Golan D, Somer E, Dishon S, Cuzin-Disegni L, Miller A. Impact of exposure to war stress on exacerbations of multiple sclerosis. *Annals of Neurology.* Aug 2008;64(2):143-148.
47. Golan D, Staun-Ram E, Glass-Marmor L, et al. The influence of vitamin D supplementation on melatonin status in patients with multiple sclerosis. *Brain Behav Immun.* Aug 2013;32:180-185.
48. Harrison T, Stuifbergen A, Adachi E, Becker H. Marriage, impairment, and acceptance in persons with multiple sclerosis. *Western Journal of Nursing Research.* Apr 2004;26(3):266-285; discussion 286-292.
49. Hart S, Fonareva I, Merluzzi N, Mohr DC. Treatment for depression and its relationship to improvement in quality of life and psychological well-being in multiple sclerosis patients. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation.* Apr 2005;14(3):695-703.
50. Hayes HA, Gappmaier E, LaStayo PC. Effects of high-intensity resistance training on strength, mobility, balance, and fatigue in individuals with multiple sclerosis: a randomized controlled trial. *Journal of Neurologic Physical Therapy: JNPT.* Mar 2011;35(1):2-10.
51. Hellwig K, Haghikia A, Rockhoff M, Gold R. Multiple sclerosis and pregnancy: experience from a nationwide database in Germany. *Ther Adv Neurol Disord.* Sep 2012;5(5):247-253.
52. Helmick CG, Wrigley JM, Zack MM, et al. Multiple sclerosis in Key West, Florida. *American Journal of Epidemiology.* Nov 1989;130(5):935-949.
53. Hilgers C, Mundermann A, Riehle H, Dettmers C. Effects of whole-body vibration training on physical function in patients with multiple sclerosis. *NeuroRehabilitation.* 2013;32(3):655-663.
54. Holmqvist P, Wallberg M, Hammar M, Landtblom AM, Brynhildsen J. Symptoms of multiple sclerosis in women in relation to sex steroid exposure. *Maturitas.* May 20 2006;54(2):149-153.
55. Jones F, Fletcher B. Occupational factors in multiple sclerosis: An analysis of occupational mortality statistics for men and married women in Great Britain. *Neuroepidemiology.* Jul-Aug 1996;15(4):222-228.
56. Julian LJ, Vella L, Vollmer T, Hadjimichael O, Mohr DC. Employment in multiple sclerosis. Exiting and re-entering the work force. *Journal of Neurology.* Sep 2008;255(9):1354-1360.
57. Khalili M, Eghtesadi S, Mirshafiey A, et al. Effect of lipoic acid consumption on oxidative stress among multiple sclerosis patients: a randomized controlled clinical trial. *Nutritional Neuroscience.* Jan 2014;17(1):16-20.
58. Khurana SR, Bamer AM, Turner AP, et al. The prevalence of overweight and obesity in veterans with multiple sclerosis. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists.* Feb 2009;88(2):83-91.
59. Klaren RE, Hubbard EA, Motl RW. Efficacy of a Behavioral Intervention for Reducing Sedentary Behavior in Persons with Multiple Sclerosis A Pilot Examination. *Am. J. Prev. Med.* Nov 2014;47(5):613-616.
60. Klaren RE, Motl RW, Dlugonski D, Sandroff BM, Pilutti LA. Objectively quantified physical activity in

persons with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation.* Dec 2013;94(12):2342-2348.
61. Klefbeck B, Hamrah Nedjad J. Effect of inspiratory muscle training in patients with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation.* Jul 2003;84(7):994-999.
62. Koch M, Uyttenboogaart M, van Harten A, De Keyser J. Factors associated with the risk of secondary progression in multiple sclerosis. *Mult. Scler. J.* Jul 2008;14(6):799-803.
63. Kremenchutzky M, Rice GPA, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study - 9: Observations on the progressive phase of the disease. *Brain: A Journal of Neurology.* Mar 2006;129:584-594.
64. Krokavcova M, van Dijk JP, Nagyova I, et al. Social support as a predictor of perceived health status in patients with multiple sclerosis. *Patient Education and Counseling.* Oct 2008;73(1):159-165.
65. Kurtzke JF. Some epidemiologic features compatible with an infectious origin for multiple sclerosis. *International Archives of Allergy and Applied Immunology.* 1969;36:Suppl:59-82.
66. Kurtzke JF. MS epidemiology world wide. One view of current status. *Acta Neurologica Scandinavica. Supplementum.* 1995;161:23-33.
67. Kurtzke JF. Epidemiology of multiple sclerosis. Does this really point toward an etiology? Lectio Doctoralis. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology.* Dec 2000;21(6):383-403.
68. Kurtzke JF, Beebe GW, Nagler B, Auth TL, Kurland LT, Nefzger MD. Studies on natural history of multiple sclerosis. 4. Clinical features of the onset bout. *Acta Neurologica Scandinavica.* 1968;44(4):467-494.
69. Kurtzke JF, Beebe GW, Norman JE, Jr. Epidemiology of multiple sclerosis in U.S. veterans: 1. Race, sex, and geographic distribution. *Neurology.* Sep 1979;29(9 Pt 1):1228-1235.
70. Kurtzke JF, Beebe GW, Norman JE, Jr. Epidemiology of multiple sclerosis in US veterans: III. Migration and the risk of MS. *Neurology.* May 1985;35(5):672-678.
71. Kurtzke JF, Page WF. Epidemiology of multiple sclerosis in US veterans: VII. Risk factors for MS. *Neurology.* Jan 1997;48(1):204-213.
72. Kurtzke JF, Page WF, Murphy FM, Norman JE, Jr. Epidemiology of multiple sclerosis in US veterans. 4. Age at onset. *Neuroepidemiology.* 1992;11(4-6):226-235.
73. Langer-Gould A, Huang S, Van Den Eeden SK, et al. Vitamin D, Pregnancy, Breastfeeding, and Postpartum Multiple Sclerosis Relapses. *Archives of Neurology.* Mar 2011;68(3):310-313.
74. Lauer K. The risk of multiple sclerosis in the U.S.A. in relation to sociogeographic features: a factor-analytic study. *Journal of Clinical Epidemiology.* Jan 1994;47(1):43-48.
75. Lavela SL, Prohaska TR, Furner S, Weaver FM. Chronic diseases in male veterans with multiple sclerosis. *Preventing Chronic Disease.* 2012;9:E55.
76. Learmonth YC, Paul L, Miller L, Mattison P, McFadyen AK. The effects of a 12-week leisure centre-based, group exercise intervention for people moderately affected with multiple sclerosis: a randomized controlled pilot study. *Clin Rehabil.* Jul 2012;26(7):579-593.
77. Leong EM, Semple SJ, Angley M, Siebert W, Petkov J, McKinnon RA. Complementary and alternative medicines and dietary interventions in multiple sclerosis: What is being used in South Australia and why? *Complementary Therapies in Medicine.* Aug 2009;17(4):216-223.
78. Lotfi J, Sahraian MA, Khorramnia S, Ebrahim MM. Effects of pregnancy on the disease course in Iranian multiple sclerosis patients. *Multiple Sclerosis.* Sep 2008;14:S143-S144.
79. Lozano-Quilis JA, Gil-Gomez H, Gil-Gomez JA, et al. Virtual Rehabilitation for Multiple Sclerosis Using a Kinect-Based System: Randomized Controlled Trial. *J. Med. Internet Res.* Nov 2014;16(11).
80. Lucas RM, Ponsonby AL, Dear K, et al. Sun exposure and vitamin D are independent risk factors for CNS demyelination. *Neurology.* Feb 8 2011;76(6):540-548.
81. Mackereth PA, Booth K, Hillier VF, Caress AL. Reflexology and progressive muscle relaxation training for people with multiple sclerosis: a crossover trial. *Complementary Therapies in Clinical Practice.* Feb 2009;15(1):14-21.
82. Marandi SM, Nejad VS, Shanazari Z, Zolaktaf V. A comparison of 12 weeks of pilates and aquatic training on the dynamic balance of women with mulitple sclerosis. *International Journal of Preventive Medicine.* Apr 2013;4(Suppl 1):S110-117.
83. Marrie RA, Horwitz RI, Cutter G, Tyry T, Vollmer T. Association between comorbidity and clinical characteristics of MS. *Acta Neurologica Scandinavica.* Aug 2011;124(2):135-141.
84. McAuley E, Motl RW, Morris KS, et al. Enhancing physical activity adherence and well-being in multiple sclerosis: a randomised controlled trial. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jun

2007;13(5):652-659.
85. McCullagh R, Fitzgerald AP, Murphy RP, Cooke G. Long-term benefits of exercising on quality of life and fatigue in multiple sclerosis patients with mild disability: a pilot study. *Clin Rehabil.* Mar 2008;22(3):206-214.
86. McDowell TY, Amr S, Culpepper WJ, et al. Sun exposure, vitamin D and age at disease onset in relapsing multiple sclerosis. *Neuroepidemiology.* 2011;36(1):39-45.
87. McDowell TY, Amr S, Langenberg P, et al. Time of birth, residential solar radiation and age at onset of multiple sclerosis. *Neuroepidemiology.* 2010;34(4):238-244.
88. Medina-Perez C, de Souza-Teixeira F, Fernandez-Gonzalo R, de Paz-Fernandez JA. Effects of a resistance training program and subsequent detraining on muscle strength and muscle power in multiple sclerosis patients. *NeuroRehabilitation.* 2014;34(3):523-530.
89. Mills N, Allen J. Mindfulness of movement as a coping strategy in multiple sclerosis. A pilot study. *Gen Hosp Psychiatry.* Nov-Dec 2000;22(6):425-431.
90. Mod RW, Snook EM, McAuley E, Scott JA, Gliottoni RC. Are physical activity and symptoms correlates of functional limitations and disability in multiple sclerosis? *Rehabilitation Psychology.* Nov 2007;52(4):463-469.
91. Mohr DC, Goodkin DE, Islar J, Hauser SL, Genain CP. Treatment of depression is associated with suppression of nonspecific and antigen-specific T(H)1 responses in multiple sclerosis. *Archives of Neurology.* Jul 2001;58(7):1081-1086.
92. Morrison W, Nelson J. Environmental triggers in multiple sclerosis. Fact or fallacy? *Axone.* Sep 1994;16(1):23-26.
93. Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2002;8(2):161-168.
94. Motl RW, Dlugonski D, Wojcicki TR, McAuley E, Mohr DC. Internet intervention for increasing physical activity in persons with multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jan 2011;17(1):116-128.
95. Motl RW, McAuley E, Snook EM. Physical activity and multiple sclerosis: a meta-analysis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Aug 2005;11(4):459-463.
96. Motl RW, Pilutti LA, Learmonth YC, Goldman MD, Brown T. Clinical Importance of Steps Taken per Day among Persons with Multiple Sclerosis. *PloS One.* Sep 2013;8(9).
97. Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. *Neurology.* Nov 10 2009;73(19):1543-1550.
98. Negahban H, Rezaie S, Goharpey S. Massage therapy and exercise therapy in patients with multiple sclerosis: a randomized controlled pilot study. *Clin Rehabil.* Dec 2013;27(12):1126-1136.
99. Nelson RE, Xie Y, Kamauu A, Schuerch M, Foskett N, Lafleur J. Multiple sclerosis increases the risk of infections resulting in a hospitalization among veterans. *Value in Health.* May 2013;16(3):A79-A80.
100. Neuteboom RF, Janssens AC, Siepman TA, et al. Pregnancy in multiple sclerosis: clinical and self-report scales. *Journal of Neurology.* Feb 2012;259(2):311-317.
101. Nilsagard YE, Forsberg AS, von Koch L. Balance exercise for persons with multiple sclerosis using Wii games: a randomised, controlled multi-centre study. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Feb 2013;19(2):209-216.
102. Nisipeanu P, Korczyn AD. Psychological stress as risk factor for exacerbations in multiple sclerosis. *Neurology.* Jul 1993;43(7):1311-1312.
103. Norman JE, Jr., Cook SD, Dowling PC. Household pets among veterans with multiple sclerosis and age-matched controls. Pilot survey. *Archives of Neurology.* Apr 1983;40(4):213-214.
104. Norman JE, Jr., Kurtzke JF, Beebe GW. Epidemiology of multiple sclerosis in U.S. veterans: 2. Latitude, climate and the risk of multiple sclerosis. *Journal of Chronic Diseases.* 1983;36(8):551-559.
105. O'Connor K, Weinstock-Guttman B, Carl E, Kilanowski C, Zivadinov R, Ramanathan M. Patterns of dietary and herbal supplement use by multiple sclerosis patients. *Journal of Neurology.* Apr 2012;259(4):637-644.
106. Oken BS, Kishiyama S, Zajdel D, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. *Neurology.* Jun 8 2004;62(11):2058-2064.
107. Page WF, Kurtzke JF, Murphy FM, Norman JE, Jr. Epidemiology of multiple sclerosis in U.S. veterans: V. Ancestry and the risk of multiple sclerosis. *Annals of Neurology.* Jun 1993;33(6):632-639.
108. Page WF, Mack TM, Kurtzke JF, Murphy FM, Norman JE, Jr. Epidemiology of multiple sclerosis in US veterans. 6. Population ancestry and surname ethnicity as risk factors for multiple sclerosis.

*Neuroepidemiology.* 1995;14(6):286-296.
109. Pilutti LA, Dlugonski D, Sandroff BM, Klaren R, Motl RW. Randomized controlled trial of a behavioral intervention targeting symptoms and physical activity in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2014;20(5):594-601.
110. Pilutti LA, Dlugonski D, Sandroff BM, Klaren RE, Motl RW. Internet-delivered lifestyle physical activity intervention improves body composition in multiple sclerosis: preliminary evidence from a randomized controlled trial. *Archives of Physical Medicine and Rehabilitation.* Jul 2014;95(7):1283-1288.
111. Plow M, Bethoux F, Mai K, Marcus B. A formative evaluation of customized pamphlets to promote physical activity and symptom self-management in women with multiple sclerosis. *Health Educ. Res.* Oct 2014;29(5):883-896.
112. Plow M, Bethoux F, McDaniel C, McGlynn M, Marcus B. Randomized controlled pilot study of customized pamphlets to promote physical activity and symptom self-management in women with multiple sclerosis. *Clin Rehabil.* Feb 2014;28(2):139-148.
113. Portaccio E, Ghezzi A, Hakiki B, et al. Breastfeeding is not related to postpartum relapses in multiple sclerosis. *Neurology.* Jul 12 2011;77(2):145-150.
114. Purdey M. Chronic barium intoxication disrupts sulphated proteoglycan synthesis: a hypothesis for the origins of multiple sclerosis. *Medical Hypotheses.* 2004;62(5):746-754.
115. Ross RT, Cheang M. Geographic similarities between varicella and multiple sclerosis: an hypothesis on the environmental factor of multiple sclerosis. *Journal of Clinical Epidemiology.* Jun 1995;48(6):731-737.
116. Rudick RA, Lee JC, Cutter GR, et al. Disability progression in a clinical trial of relapsing-remitting multiple sclerosis: eight-year follow-up. *Archives of Neurology.* Nov 2010;67(11):1329-1335.
117. Ruiz J, Labas MP, Triche EW, Lo AC. Combination of robot-assisted and conventional body-weight-supported treadmill training improves gait in persons with multiple sclerosis: a pilot study. *Journal of neurologic physical therapy: JNPT.* Dec 2013;37(4):187-193.
118. Runia TF, Hop WC, de Rijke YB, Buljevac D, Hintzen RQ. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. *Neurology.* Jul 17 2012;79(3):261-266.
119. Sabapathy NM, Minahan CL, Turner GT, Broadley SA. Comparing endurance- and resistance-exercise training in people with multiple sclerosis: a randomized pilot study. *Clin Rehabil.* Jan 2011;25(1):14-24.
120. Sadovnick AD, Eisen K, Hashimoto SA, et al. Pregnancy and multiple sclerosis. A prospective study. *Archives of Neurology.* Nov 1994;51(11):1120-1124.
121. Sandroff BM, Klaren RE, Pilutti LA, Dlugonski D, Benedict RH, Motl RW. Randomized controlled trial of physical activity, cognition, and walking in multiple sclerosis. *Journal of Neurology.* Feb 2014;261(2):363-372.
122. Sibley WA, Bamford CR, Clark K. Clinical viral infections and multiple sclerosis. *Lancet.* Jun 8 1985;1(8441):1313-1315.
123. Somer E, Golan D, Dishon S, Cuzin-Disegni L, Lavi I, Miller A. Patients with multiple sclerosis in a war zone: coping strategies associated with reduced risk for relapse. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2010;16(4):463-471.
124. Sosnoff JJ, Finlayson M, McAuley E, Morrison S, Motl RW. Home-based exercise program and fall-risk reduction in older adults with multiple sclerosis: phase 1 randomized controlled trial. *Clin Rehabil.* Mar 2014;28(3):254-263.
125. Stoll SS, Nieves C, Tabby DS, Schwartzman R. Use of therapies other than disease-modifying agents, including complementary and alternative medicine, by patients with multiple sclerosis: a survey study. *The Journal of the American Osteopathic Association.* Jan 2012;112(1):22-28.
126. Straudi S, Benedetti MG, Venturini E, Manca M, Foti C, Basaglia N. Does robot-assisted gait training ameliorate gait abnormalities in multiple sclerosis? A pilot randomized-control trial. *NeuroRehabilitation.* 2013;33(4):555-563.
127. Stuifbergen AK, Roberts GJ. Health promotion practices of women with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation.* Dec 1997;78(12 Suppl 5):S3-9.
128. Surakka J, Romberg A, Ruutiainen J, et al. Effects of aerobic and strength exercise on motor fatigue in men and women with multiple sclerosis: a randomized controlled trial. *Clin Rehabil.* Nov 2004;18(7):737-746.
129. Sutherland G, Andersen MB, Morris T. Relaxation and health-related quality of life in multiple sclerosis: the example of autogenic training. *Journal of Behavioral Medicine.* Jun 2005;28(3):249-256.
130. Sutherland G, Andersen MB, Stoove MA. Can aerobic exercise training affect health-related quality of life for people with multiple sclerosis? *J. Sport Exerc. Psychol.* Jun 2001;23(2):122-135.
131. Tarakci E, Yeldan I, Huseyinsinoglu BE, Zenginler Y, Eraksoy M. Group exercise training for balance, functional status, spasticity, fatigue and quality of life in multiple sclerosis: a randomized controlled trial.

*Clin Rehabil.* Sep 2013;27(9):813-822.
132. Tedeholm H, Skoog B, Lisovskaja V, Runmarker B, Nerman O, Andersen O. The outcome spectrum of multiple sclerosis: disability, mortality, and a cluster of predictors from onset. *Journal of Neurology.* Feb 26 2015.
133. Tesar N, Bandion K, Baumhackl U. Efficacy of a neuropsychological training programme for patients with multiple sclerosis -- a randomised controlled trial. *Wiener Klinische Wochenschrift.* Nov 2005;117(21-22):747-754.
134. Tinghog P, Bjorkenstam C, Carstensen J, et al. Co-morbidities increase the risk of disability pension among MS patients: a population-based nationwide cohort study. *BMC Neurol.* 2014;14:117.
135. Tosh J, Dixon S, Carter A, et al. Cost effectiveness of a pragmatic exercise intervention (EXIMS) for people with multiple sclerosis: economic evaluation of a randomised controlled trial. *Mult. Scler. J.* Jul 2014;20(8):1123-1130.
136. Turner AP, Hartoonian N, Maynard C, Leipertz SL, Haselkorn JK. Examining Health Behaviors and 15 year Mortality among Individuals with Multiple Sclerosis. *Archives of Physical Medicine and Rehabilitation.* Nov 6 2014.
137. Turner AP, Hartoonian N, Maynard C, Leipertz SL, Haselkorn JK. Smoking and physical activity: examining health behaviors and 15-year mortality among individuals with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation.* Mar 2015;96(3):402-409.
138. Turner AP, Hawkins EJ, Haselkorn JK, Kivlahan DR. Alcohol misuse and multiple sclerosis. *Archives of Physical Medicine and Rehabilitation.* May 2009;90(5):842-848.
139. Turner AP, Kivlahan DR, Haselkorn JK. Exercise and quality of life among people with multiple sclerosis: looking beyond physical functioning to mental health and participation in life. *Archives of Physical Medicine and Rehabilitation.* Mar 2009;90(3):420-428.
140. Turner AP, Kivlahan DR, Kazis LE, Haselkorn JK. Smoking among veterans with multiple sclerosis: prevalence correlates, quit attempts, and unmet need for services. *Archives of Physical Medicine and Rehabilitation.* Nov 2007;88(11):1394-1399.
141. Turner AP, Williams RM, Bowen JD, Kivlahan DR, Haselkorn JK. Suicidal ideation in multiple sclerosis. *Archives of Physical Medicine and Rehabilitation.* Aug 2006;87(8):1073-1078.
142. Tyler ME, Kaczmarek KA, Rust KL, Subbotin AM, Skinner KL, Danilov YP. Non-invasive neuromodulation to improve gait in chronic multiple sclerosis: a randomized double blind controlled pilot trial. *J Neuroeng Rehabil.* 2014;11:79.
143. van den Berg M, Dawes H, Wade DT, et al. Treadmill training for individuals with multiple sclerosis: a pilot randomised trial. *Journal of Neurology, Neurosurgery, and Psychiatry.* Apr 2006;77(4):531-533.
144. van der Mei IA, Ponsonby AL, Dwyer T, et al. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. *BMJ.* Aug 9 2003;327(7410):316.
145. Vaney C, Gattlen B, Lugon-Moulin V, et al. Robotic-assisted step training (lokomat) not superior to equal intensity of over-ground rehabilitation in patients with multiple sclerosis. *Neurorehabil Neural Repair.* Mar-Apr 2012;26(3):212-221.
146. Velikonja O, Curic K, Ozura A, Jazbec SS. Influence of sports climbing and yoga on spasticity, cognitive function, mood and fatigue in patients with multiple sclerosis. *Clinical Neurology and Neurosurgery.* Sep 2010;112(7):597-601.
147. Wallin MT, Culpepper WJ, Coffman P, et al. The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service. *Brain: A Journal of Neurology.* Jun 2012;135(Pt 6):1778-1785.
148. Wallin MT, Kurtzke JF, Culpepper WJ, et al. Multiple sclerosis in gulf war era veterans. 2. Military deployment and risk of multiple sclerosis in the first gulf war. *Neuroepidemiology.* 2014;42(4):226-234.
149. Wallin MT, Page WF, Kurtzke JF. Epidemiology of multiple sclerosis in US veterans. VIII. Long-term survival after onset of multiple sclerosis. *Brain: A Journal of Neurology.* Aug 2000;123 ( Pt 8):1677-1687.
150. Wallin MT, Page WF, Kurtzke JF. Multiple sclerosis in US veterans of the Vietnam era and later military service: race, sex, and geography. *Annals of Neurology.* Jan 2004;55(1):65-71.
151. Wallin MT, Page WF, Kurtzke JF. Migration and multiple sclerosis in Alaskan military veterans. *Journal of Neurology.* Sep 2009;256(9):1413-1417.
152. Wang L, Li L, Zhang J, Baser O. Comorbidities and economic burden of multiple sclerosis patients in the united states veteran population. *Value in Health.* May 2013;16(3):A101.
153. Weikert M, Motl RW, Mohr DC. Associations among physical activity, stress, disability, and relapse occurrence in multiple sclerosis. *Mult. Scler. J.* Aug 2010;16(8):1020-1020.
154. Weiland TJ, Jelinek GA, Marck CH, et al. Clinically Significant Fatigue: Prevalence and Associated Factors in an International Sample of Adults with Multiple Sclerosis Recruited via the Internet. *PloS One.*

2015;10(2):e0115541.
155. Widener GL, Allen DD, Gibson-Horn C. Randomized clinical trial of balance-based torso weighting for improving upright mobility in people with multiple sclerosis. *Neurorehabil Neural Repair.* Oct 2009;23(8):784-791.
156. Williams RM, Turner AP, Hatzakis M, Jr., Bowen JD, Rodriquez AA, Haselkorn JK. Prevalence and correlates of depression among veterans with multiple sclerosis. *Neurology.* Jan 11 2005;64(1):75-80.
157. Yamout B, Itani S, Hourany R, Sibaii AM, Yaghi S. The effect of war stress on multiple sclerosis exacerbations and radiological disease activity. *Journal of the Neurological Sciences.* Jan 15 2010;288(1-2):42-44.
158. Yildiz M, Tettenborn B, Putzki N. Vitamin D levels in Swiss multiple sclerosis patients. *Swiss Med Wkly.* 2011;141:w13192.
159. Zeqiraj K, Kruja J, Kabashi S, Mucaj S. Epidemiological characteristics and functional disability of multiple sclerosis patients in Kosovo. *Medicinski Arhiv.* 2014;68(3):178-181.

## EXCLUDE: INTERVENTION/EXPOSURE

Publications not reporting on a risk factor of interest:

1. Aisen ML, Sevilla D, Fox N. Inpatient rehabilitation for multiple sclerosis. *J. Neurol. Rehabil.* 1996;10(1):43-46.
2. Akhtar N, Elsetouhy A, Deleu D, et al. Newly diagnosed multiple sclerosis in state of Qatar. *Clinical Neurology and Neurosurgery.* Aug 2013;115(8):1333-1337.
3. Amato MP, Ponziani G. A prospective study on the prognosis of multiple sclerosis. *Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology.* 2000;21(4 Suppl 2):S831-838.
4. Artemiadis AK, Vervainioti AA, Alexopoulos EC, Rombos A, Anagnostouli MC, Darviri C. Stress management and multiple sclerosis: a randomized controlled trial. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists.* Jun 2012;27(4):406-416.
5. Ashtari F, Ajalli M, Shaygannejad V, Akbari M, Hovsepian S. The relation between Vitamin D status with fatigue and depressive symptoms of multiple sclerosis. *Journal of research in medical sciences: The Official Journal of Isfahan University of Medical Sciences.* Mar 2013;18(3):193-197.
6. Askari F, Ghajarzadeh M, Mohammadifar M, Azimi A, Sahraian MA, Owji M. Anxiety in patients with multiple sclerosis: association with disability, depression, disease type and sex. *Acta Medica Iranica.* 2014;52(12):889-892.
7. Baumhackl U, Kappos L, Radue EW, et al. A randomized, double-blind, placebo-controlled study of oral hydrolytic enzymes in relapsing multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2005;11(2):166-168.
8. Baumstarck K, Pelletier J, Butzkueven H, et al. Health-related quality of life as an independent predictor of long-term disability for patients with relapsing-remitting multiple sclerosis. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies.* Jun 2013;20(6):907-914, e978-909.
9. Benito-Leon J, Mitchell AJ, Rivera-Navarro J, Morales-Gonzalez JM. Impaired health-related quality of life predicts progression of disability in multiple sclerosis. *European journal of neurology: the official journal of the European Federation of Neurological Societies.* Jan 2013;20(1):79-86.
10. Bergamaschi R, Berzuini C, Romani A, Cosi V. Predicting secondary progression in relapsing-remitting multiple sclerosis: a Bayesian analysis. *Journal of the Neurological Sciences.* Aug 15 2001;189(1-2):13-21.
11. Berg-Hansen P, Smestad C, Sandvik L, Harbo HF, Celius EG. Increased disease severity in non-Western immigrants with multiple sclerosis in Oslo, Norway. *European Journal of Neurology.* Dec 2013;20(12):1546-1552.
12. Broadley SA, Vanags D, Williams B, et al. Results of a phase IIa clinical trial of an anti-inflammatory molecule, chaperonin 10, in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Mar 2009;15(3):329-336.
13. Calabrese M, Romualdi C, Poretto V, et al. The changing clinical course of multiple sclerosis: a matter of gray matter. *Annals of Neurology.* Jul 2013;74(1):76-83.
14. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. *N Engl J Med.* Nov 16 2000;343(20):1430-1438.
15. D'Alisa S, Miscio G, Baudo S, Simone A, Tesio L, Mauro A. Depression is the main determinant of quality

of life in multiple sclerosis: a classification-regression (CART) study. *Disability and Rehabilitation.* Mar 15 2006;28(5):307-314.

16. Damasceno A, Von Glehn F, Brandao CO, Damasceno BP, Cendes F. Prognostic indicators for long-term disability in multiple sclerosis patients. *Journal of the Neurological Sciences.* Jan 15 2013;324(1-2):29-33.
17. Debouverie M, Pittion-Vouyovitch S, Louis S, Guillemin F. Natural history of multiple sclerosis in a population-based cohort. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies.* Sep 2008;15(9):916-921.
18. D'Hooghe M B, Nagels G, Uitdehaag BM. Long-term effects of childbirth in MS. *Journal of Neurology, Neurosurgery, and Psychiatry.* Jan 2010;81(1):38-41.
19. Ehde DM, Kraft GH, Chwastiak L, et al. Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis. *Gen Hosp Psychiatry.* Jan-Feb 2008;30(1):40-48.
20. Ehrenreich H, Fischer B, Norra C, et al. Exploring recombinant human erythropoietin in chronic progressive multiple sclerosis. *Brain: A Journal of Neurology.* Oct 2007;130(Pt 10):2577-2588.
21. El-Salem K, Al-Shimmery E, Horany K, Al-Refai A, Al-Hayk K, Khader Y. Multiple sclerosis in Jordan: A clinical and epidemiological study. *Journal of Neurology.* Sep 2006;253(9):1210-1216.
22. Eriksson M, Andersen O, Runmarker B. Long-term follow up of patients with clinically isolated syndromes, relapsing-remitting and secondary progressive multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jun 2003;9(3):260-274.
23. Friedman JE, Zabriskie JB, Plank C, et al. A randomized clinical trial of valacyclovir in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jun 2005;11(3):286-295.
24. Guarnaccia JB, Aslan M, O'Connor TZ, et al. Quality of life for veterans with multiple sclerosis on disease-modifying agents: Relationship to disability. *Journal of Rehabilitation Research and Development.* Jan-Feb 2006;43(1):35-44.
25. Guerra E, di Cagno A, Mancini P, et al. Physical fitness assessment in multiple sclerosis patients: a controlled study. *Research in Developmental Disabilities.* Oct 2014;35(10):2527-2533.
26. Haas J, Hommes OR. A dose comparison study of IVIG in postpartum relapsing-remitting multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Aug 2007;13(7):900-908.
27. Hughes SE, Spelman T, Gray OM, et al. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* May 2014;20(6):739-746.
28. Kaiser CC, Shukla DK, Stebbins GT, et al. A pilot test of pioglitazone as an add-on in patients with relapsing remitting multiple sclerosis. *Journal of Neuroimmunology.* Jun 25 2009;211(1-2):124-130.
29. Kappos L, Freedman MS, Polman CH, et al. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. *Lancet.* Aug 4 2007;370(9585):389-397.
30. Karp I, Manganas A, Sylvestre MP, Roger E, Ho A, Duquette P. The impact of pregnancy on progression of relapsing-remitting multiple sclerosis. *Mult. Scler. J.* Oct 2012;18:102-103.
31. Kaufman MD, Johnson SK, Moyer D, Bivens J, Norton HJ. Multiple sclerosis: severity and progression rate in African Americans compared with whites. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists.* Aug 2003;82(8):582-590.
32. Keyhanian K, Davoudi V, Etemadifar M, Amin M. Better prognosis of multiple sclerosis in patients who experienced a full-term pregnancy. *European Neurology.* 2012;68(3):150-155.
33. Khaleeli Z, Ciccarelli O, Manfredonia F, et al. Predicting progression in primary progressive multiple sclerosis: a 10-year multicenter study. *Annals of Neurology.* Jun 2008;63(6):790-793.
34. Kimball SM, Ursell MR, O'Connor P, Vieth R. Safety of vitamin D3 in adults with multiple sclerosis. *The American Journal of Clinical Nutrition.* Sep 2007;86(3):645-651.
35. Koch M, Mostert J, Heerings M, Uyttenboogaart M, De Keyser J. Fatigue, depression and disability accumulation in multiple sclerosis: a cross-sectional study. *European Journal of Neurology.* Mar 2009;16(3):348-352.
36. Koch M, Ramsaransing GS, Fokkema MR, Heersema DJ, De Keyser J. Erythrocyte membrane fatty acids in benign and progressive forms of multiple sclerosis. *Journal of the Neurological Sciences.* May 15 2006;244(1-2):123-126.
37. Koch M, Uyttenboogaart M, Heerings M, Heersema D, Mostert J, De Keyser J. Progression in familial and nonfamilial MS. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2008;14(3):300-306.
38. Koch M, Uyttenboogaart M, Heersema D, Steen C, De Keyser J. Parity and secondary progression in multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry.* Jun 2009;80(6):676-678.
39. Koch M, Uyttenboogaart M, van Harten A, Heerings M, De Keyser J. Fatigue, depression and progression in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jul 2008;14(6):815-822.

40. Koch MW, Patten S, Berzins S, et al. Depression in multiple sclerosis: A long-term longitudinal study. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jan 2015;21(1):76-82.
41. Kochs L, Wegener S, Suhnel A, Voigt K, Zettl UK. The use of complementary and alternative medicine in patients with multiple sclerosis: a longitudinal study. *Complementary Therapies in Medicine.* Feb 2014;22(1):166-172.
42. Kurtzke JF, Auth TL, Beebe GW, Kurland LT, Nagler B, Nefzger MD. Survival in multiple sclerosis. *Transactions of the American Neurological Association.* 1969;94:134-139.
43. Kurtzke JF, Beebe GW, Nagler B, Nefzger MD, Auth TL, Kurland LT. Studies on the natural history of multiple sclerosis. V. Long-term survival in young men. *Archives of Neurology.* Mar 1970;22(3):215-225.
44. Lambert CP, Lee Archer R, Evans WJ. Body composition in ambulatory women with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation.* Nov 2002;83(11):1559-1561.
45. Lincoln NB, Yuill F, Holmes J, et al. Evaluation of an adjustment group for people with multiple sclerosis and low mood: a randomized controlled trial. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Oct 2011;17(10):1250-1257.
46. Locke S, Kruper DC, Yakovlev PI. FIVE-YEAR FOLLOW-UP ON MULTIPLE SCLEROSIS. REPORT ON VETERANS ADMINISTRATION COOPERATIVE STUDY. *Archives of Neurology.* Dec 1964;11:583-592.
47. Lucas RM, Hughes AM, Lay ML, et al. Epstein-Barr virus and multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry.* Oct 2011;82(10):1142-1148.
48. Mandel M, Gauthier SA, Guttmann CRG, Weiner HL, Betensky RA. Estimating time to event from longitudinal categorical data: An analysis of multiple sclerosis progression. *J. Am. Stat. Assoc.* Dec 2007;102(480):1254-1266.
49. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. Comorbidity delays diagnosis and increases disability at diagnosis in MS. *Neurology.* Jan 13 2009;72(2):117-124.
50. Marrie RA, Rudick R, Horwitz R, et al. Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. *Neurology.* Mar 2010;74(13):1041-1047.
51. Masera S, Cavalla P, Prosperini L, et al. Parity is associated with a longer time to reach irreversible disability milestones in women with multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Dec 22 2014.
52. Masera S, Prosperini L, Petsas N, et al. Multiple sclerosis and pregnancy: relationship with progression of disability. *Multiple Sclerosis.* Sep 2008;14:S192-S192.
53. Mastorodemos V, Nikolakaki H, Tzagournissakis M, et al. Benign multiple sclerosis in Crete. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jun 2010;16(6):701-706.
54. Menzin J, Caon C, Nichols C, White LA, Friedman M, Pill MW. Narrative Review of the Literature on Adherence to Disease-Modifying Therapies Among Patients with Multiple Sclerosis. *Journal of Managed Care Pharmacy.* Jan-Feb 2013;19(1):S24-S40.
55. Milanlioglu A, Ozdemir PG, Cilingir V, Gulec TC, Aydin MN, Tombul T. Coping strategies and mood profiles in patients with multiple sclerosis. *Arq Neuropsiquiatr.* Jul 2014;72(7):490-495.
56. Mitsonis CI, Zervas IM, Potagas CM, et al. Effects of escitalopram on stress-related relapses in women with multiple sclerosis: an open-label, randomized, controlled, one-year follow-up study. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology.* Feb 2010;20(2):123-131.
57. Moghaddasi M, Mamarabadi M, Mohebi N, Razjouyan H, Aghaei M. Homocysteine, vitamin B12 and folate levels in Iranian patients with Multiple Sclerosis: A case control study. *Clinical Neurology and Neurosurgery.* 2013;115(9):1802-1805.
58. Mohr DC, Boudewyn AC, Goodkin DE, Bostrom A, Epstein L. Comparative outcomes for individual cognitive-behavior therapy, supportive-expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. *Journal of Consulting and Clinical Psychology.* Dec 2001;69(6):942-949.
59. Mohr DC, Hart S, Vella L. Reduction in disability in a randomized controlled trial of telephone-administered cognitive-behavioral therapy. *Health psychology: official journal of the Division of Health Psychology, American Psychological Association.* Sep 2007;26(5):554-563.
60. Mutluay FK, Demir R, Ozyilmaz S, Caglar AT, Altintas A, Gurses HN. Breathing-enhanced upper extremity exercises for patients with multiple sclerosis. *Clin Rehabil.* Jul 2007;21(7):595-602.
61. Nelson RE, Xie Y, Du Vall SL, et al. Multiple sclerosis subtypes and infections resulting in a hospitalization in the veterans health administration. *Pharmacoepidemiology and Drug Safety.* October 2013;22 SUPPL. 1:406.
62. Patti F, Ciancio MR, Cacopardo M, et al. Effects of a short outpatient rehabilitation treatment on disability

of multiple sclerosis patients--a randomised controlled trial. *Journal of Neurology.* Jul 2003;250(7):861-866.
63. Patti F, Ciancio MR, Reggio E, et al. The impact of outpatient rehabilitation on quality of life in multiple sclerosis. *Journal of Neurology.* Aug 2002;249(8):1027-1033.
64. Pilutti LA. Adapted exercise interventions for persons with progressive multiple sclerosis. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition et Metabolisme.* Mar 2013;38(3):357.
65. Pilutti LA, Lelli DA, Paulseth JE, et al. Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: a pilot study. *Archives of Physical Medicine and Rehabilitation.* Jan 2011;92(1):31-36.
66. Pittock SJ, Mayr WT, McClelland RL, et al. Change in MS-related disability in a population-based cohort: a 10-year follow-up study. *Neurology.* Jan 13 2004;62(1):51-59.
67. Pohlau D, Przuntek H, Sailer M, et al. Intravenous immunoglobulin in primary and secondary chronic progressive multiple sclerosis: a randomized placebo controlled multicentre study. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Nov 2007;13(9):1107-1117.
68. Ponichtera JA, Rodgers MM, Glaser RM, Mathews TA, Camaione DN. Concentric and eccentric isokinetic lower extremity strength in persons with multiple sclerosis. *The Journal of Orthopaedic and Sports Physical Therapy.* 1992;16(3):114-122.
69. Pozzilli C, Palmisano L, Mainero C, et al. Relationship between emotional distress in caregivers and health status in persons with multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Aug 2004;10(4):442-446.
70. Ramagopalan S, Yee I, Byrnes J, Guimond C, Ebers G, Sadovnick D. Term pregnancies and the clinical characteristics of multiple sclerosis: a population based study. *Journal of Neurology, Neurosurgery, and Psychiatry.* Aug 2012;83(8):793-795.
71. Riise T, Gronning M, Fernandez O, et al. Early prognostic factors for disability in multiple sclerosis, a European multicenter study. *Acta Neurologica Scandinavica.* Mar 1992;85(3):212-218.
72. Rinker IJR, Cossey TC, Cutter GR, Culpepper WJ. A retrospective review of lithium usage in veterans with multiple sclerosis. *Multiple Sclerosis and Related Disorders.* October 2013;2(4):327-333.
73. Romberg A, Virtanen A, Aunola S, Karppi SL, Karanko H, Ruutiainen J. Exercise capacity, disability and leisure physical activity of subjects with multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Apr 2004;10(2):212-218.
74. Roullet E, Verdier-Taillefer MH, Amarenco P, Gharbi G, Alperovitch A, Marteau R. Pregnancy and multiple sclerosis: a longitudinal study of 125 remittent patients. *Journal of Neurology, Neurosurgery, and Psychiatry.* Oct 1993;56(10):1062-1065.
75. Runmarker B, Andersen O. Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. *Brain: A Journal of Neurology.* Feb 1995;118 ( Pt 1):253-261.
76. Runmarker B, Andersson C, Oden A, Andersen O. Prediction of outcome in multiple sclerosis based on multivariate models. *Journal of Neurology.* Oct 1994;241(10):597-604.
77. Salhofer-Polanyi S, Windt J, Sumper H, et al. Benefits of inpatient multidisciplinary rehabilitation in multiple sclerosis. *NeuroRehabilitation.* 2013;33(2):285-292.
78. Samonds RJ, Cammermeyer M. Perceptions of body image in subjects with multiple sclerosis: a pilot study. *The Journal of Neuroscience Nursing: Journal of the American Association of Neuroscience Nurses.* Jun 1989;21(3):190-194.
79. Sarraf P, Azizi S, Moghaddasi AN, Sahraian MA, Tafakhori A, Ghajarzadeh M. Relationship between Sleep Quality and Quality of Life in Patients with Multiple Sclerosis. *International Journal of Preventive Medicine.* Dec 2014;5(12):1582-1586.
80. Schroeder B, Doig J, Premkumar K. The effects of massage therapy on multiple sclerosis patients' quality of life and leg function. *Evidence-based Complementary and Alternative Medicine: eCAM.* 2014;2014:640916.
81. Schwartz CE, Foley FW, Rao SM, Bernardin LJ, Lee H, Genderson MW. Stress and course of disease in multiple sclerosis. *Behavioral Medicine (Washington, D.C.).* Fall 1999;25(3):110-116.
82. Sorgun MH, Yucesan C, Tegin C. Is malnutrition a problem for multiple sclerosis patients? *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia.* Sep 2014;21(9):1603-1605.
83. Stenager E, Stenager EN, Jensen K. Effect of pregnancy on the prognosis for multiple sclerosis. A 5-year follow up investigation. *Acta Neurologica Scandinavica.* Nov 1994;90(5):305-308.
84. Stroud N, Minahan C, Sabapathy S. The perceived benefits and barriers to exercise participation in persons

with multiple sclerosis. *Disability and Rehabilitation.* 2009;31(26):2216-2222.
85. Tan H, Cai Q, Agarwal S, Stephenson JJ, Kamat S. Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis. *Advances in Therapy.* Jan 2011;28(1):51-61.
86. Tavee J, Rensel M, Planchon SM, Butler RS, Stone L. Effects of meditation on pain and quality of life in multiple sclerosis and peripheral neuropathy: a pilot study. *International Journal of MS Care.* Winter 2011;13(4):163-168.
87. Terzi M, Kocamanoglu B, Guz H, Onar M. The Eating Attitudes in Multiple Sclerosis Patients. *J. Neurol. Sci.-Turk.* 2009;26(3):311-317.
88. Teter B, Apatoff B, Coyle P, et al. Pregnancy Related to Disability Outcomes for Women with Progressive Multiple Sclerosis. *Neurology.* Mar 2011;76(9):A610-A610.
89. Thompson DS, Nelson LM, Burns A, Burks JS, Franklin GM. The effects of pregnancy in multiple sclerosis: a retrospective study. *Neurology.* Aug 1986;36(8):1097-1099.
90. Tremlett H, Paty D, Devonshire V. The natural history of primary progressive MS in British Columbia, Canada. *Neurology.* Dec 27 2005;65(12):1919-1923.
91. Tremlett H, Yinshan Z, Devonshire V. Natural history of secondary-progressive multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2008;14(3):314-324.
92. Tremlett HL, Wiles CM, Luscombe DK. Nonprescription medicine use in a multiple sclerosis clinic population. *British Journal of Clinical Pharmacology.* Jul 2000;50(1):55-60.
93. Trojano M, Avolio C, Manzari C, et al. Multivariate analysis of predictive factors of multiple sclerosis course with a validated method to assess clinical events. *Journal of Neurology, Neurosurgery, and Psychiatry.* Mar 1995;58(3):300-306.
94. Trojano M, Pellegrini F, Paolicelli D, et al. Real-life impact of early interferon beta therapy in relapsing multiple sclerosis. *Annals of Neurology.* Oct 2009;66(4):513-520.
95. van der Linden ML, Bulley C, Geneen LJ, Hooper JE, Cowan P, Mercer TH. Pilates for people with multiple sclerosis who use a wheelchair: feasibility, efficacy and participant experiences. *Disability and Rehabilitation.* 2014;36(11):932-939.
96. Verdru P, Theys P, D'Hooghe MB, Carton H. Pregnancy and multiple sclerosis: the influence on long term disability. *Clinical Neurology and Neurosurgery.* Feb 1994;96(1):38-41.
97. Villoslada P, Arrondo G, Sepulcre J, Alegre M, Artieda J. Memantine induces reversible neurologic impairment in patients with MS. *Neurology.* May 12 2009;72(19):1630-1633.
98. Vukusic S, Confavreux C. Prognostic factors for progression of disability in the secondary progressive phase of multiple sclerosis. *Journal of the Neurological Sciences.* Feb 15 2003;206(2):135-137.
99. Wade DT, Young CA, Chaudhuri KR, Davidson DL. A randomised placebo controlled exploratory study of vitamin B-12, lofepramine, and L-phenylalanine (the "Cari Loder regime") in the treatment of multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry.* Sep 2002;73(3):246-249.
100. Weinshenker BG, Hader W, Carriere W, Baskerville J, Ebers GC. The influence of pregnancy on disability from multiple sclerosis: a population-based study in Middlesex County, Ontario. *Neurology.* Nov 1989;39(11):1438-1440.
101. Weinshenker BG, Rice GP, Noseworthy JH, Carriere W, Baskerville J, Ebers GC. The natural history of multiple sclerosis: a geographically based study. 3. Multivariate analysis of predictive factors and models of outcome. *Brain: A Journal of Neurology.* Apr 1991;114 ( Pt 2):1045-1056.
102. Woessner R, Grauer MT, Frese A, et al. Long-term antibiotic treatment with roxithromycin in patients with multiple sclerosis. *Infection.* Dec 2006;34(6):342-344.
103. Worthington J, Jones R, Crawford M, Forti A. Pregnancy and multiple sclerosis--a 3-year prospective study. *Journal of Neurology.* Feb 1994;241(4):228-233.
104. Yamout B, Itani S, Arabi A, Hamzeh D, Yaghi S. Prognostic factors of multiple sclerosis in Lebanon. *The International Journal of Neuroscience.* Mar 2010;120(3):206-210.
105. Zajicek J, Ball S, Wright D, et al. Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. *The Lancet. Neurology.* Sep 2013;12(9):857-865.

## EXCLUDE: DESIGN

Publications not meeting study design inclusion criteria:


1. Amezcua L, Chung RH, Conti DV, Langer-Gould AM. Vitamin D levels in Hispanics with multiple sclerosis. *Journal of Neurology.* Dec 2012;259(12):2565-2570.
2. Anens E, Emtner M, Zetterberg L, Hellstrom K. Physical activity in subjects with multiple sclerosis with focus on gender differences: a survey. *BMC Neurol.* 2014;14:47.
3. Bamford CR, Sibley WA, Laguna JF. Swine influenza vaccination in patients with multiple sclerosis. *Archives of Neurology.* Apr 1978;35(4):242-243.
4. Bhargava P, Cassard S, Steele SU, et al. The vitamin D to ameliorate multiple sclerosis (VIDAMS) trial: study design for a multicenter, randomized, double-blind controlled trial of vitamin D in multiple sclerosis. *Contemporary Clinical Trials.* Nov 2014;39(2):288-293.
5. Brichetto G, Rinaldi S, Spallarossa P, Battaglia MA, de Carvalho ML. Efficacy of physical therapy in multiple sclerosis as measured with the modified fatigue impact scale and ambulation index: a retrospective study. *NeuroRehabilitation.* 2013;33(1):107-112.
6. D'Hooghe MB, De Keyser J. Multiparity in women with multiple sclerosis causes less long-term disability: Yes. *Mult. Scler. J.* Oct 2014;20(11):1432-1434.
7. Esparza ML, Sasaki S, Kesteloot H. Nutrition, latitude, and multiple sclerosis mortality: an ecologic study. *American Journal of Epidemiology.* Oct 1 1995;142(7):733-737.
8. Farinotti M, Simi S, Di Pietrantonj C, et al. Dietary interventions for multiple sclerosis. *Cochrane Database Syst Rev.* 2007(1):Cd004192.
9. Freedman DM, Dosemeci H, Alavanja MCR. Mortality from multiple sclerosis and exposure to residential and occupational solar radiation: a case-control study based on death certificates. *Occup. Environ. Med.* Jun 2000;57(6):418-421.
10. Goodin DS. The impact of war-stress on MS exacerbations. *Annals of neurology.* Aug 2008;64(2):114-115.
11. Grant WB. Epidemiology of disease risks in relation to vitamin D insufficiency. *Prog. Biophys. Mol. Biol.* Sep 2006;92(1):65-79.
12. Griffith G, Klaren RE, Motl RW, Baynard T, Fernhall B. Experimental protocol of a randomized controlled clinical trial investigating exercise, subclinical atherosclerosis, and walking mobility in persons with multiple sclerosis. *Contemporary Clinical Trials.* Feb 14 2015.
13. Heine M, Hoogervorst EL, Hacking HG, Verschuren O, Kwakkel G. Validity of maximal exercise testing in people with multiple sclerosis and low to moderate levels of disability. *Physical Therapy.* Aug 2014;94(8):1168-1175.
14. Holmoy T, Kampman MT. Alaska, multiple sclerosis, and the vitamin D hypothesis. *Journal of Neurology.* Feb 2010;257(2):305-306.
15. Kileff J, Ashburn A. A pilot study of the effect of aerobic exercise on people with moderate disability multiple sclerosis. *Clin Rehabil.* Mar 2005;19(2):165-169.
16. Kurtzke JF. Some contributions of the Department of Veterans Affairs to the epidemiology of multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Sep 2008;14(8):1007-1012.
17. Mason RR, Cochrane DJ, Denny GJ, Firth EC, Stannard SR. Is 8 weeks of side-alternating whole-body vibration a safe and acceptable modality to improve functional performance in multiple sclerosis? *Disability and Rehabilitation.* 2012;34(8):647-654.
18. McCombe PA, Callaway LK. Multiparity in women with multiple sclerosis causes less long-term disability: No. *Mult. Scler. J.* Oct 2014;20(11):1435-1436.
19. Munoz-Lasa S, Ferriero G, Valero R, Gomez-Muniz F, Rabini A, Varela E. Effect of therapeutic horseback riding on balance and gait of people with multiple sclerosis. *Giornale Italiano di Medicina del Lavoro ed Ergonomia.* Oct-Dec 2011;33(4):462-467.
20. Namaka M, Turcotte D, Leong C, Grossberndt A, Klassen D. Multiple sclerosis: Etiology and treatment strategies. *Consultant Pharmacist.* 2008;23(11):886-896.
21. Nordvik I, Myhr KM, Nyland H, Bjerve KS. Effect of dietary advice and n-3 supplementation in newly diagnosed MS patients. *Acta Neurologica Scandinavica.* Sep 2000;102(3):143-149.
22. Ozgocmen S, Bulut S, Ilhan N, Gulkesen A, Ardicoglu O, Ozkan Y. Vitamin D deficiency and reduced bone mineral density in multiple sclerosis: effect of ambulatory status and functional capacity. *Journal of Bone and Mineral Metabolism.* 2005;23(4):309-313.
23. Pariser G, Madras D, Weiss E. Outcomes of an aquatic exercise program including aerobic capacity, lactate threshold, and fatigue in two individuals with multiple sclerosis. *Journal of neurologic physical therapy:*

*JNPT*. Jun 2006;30(2):82-90.
24. Pimentel ML. Multiple sclerosis in the Southern and Northern hemispheres: the month of birth at different latitudes has the same influence on the prevalence and progression of the disease in the Northern and Southern hemispheres? *Arq Neuropsiquiatr*. Sep 2013;71(9A):569-570.
25. Poser S, Wikstrom J, Bauer HJ. Clinical data and the identification of special forms of multiple sclerosis in 1271 cases studied with a standardized documentation system. *Journal of the Neurological Sciences*. Feb 1979;40(2-3):159-168.
26. Singh V, Hintzen RQ, Luider TM, Stoop MP. Proteomics technologies for biomarker discovery in multiple sclerosis. *Journal of Neuroimmunology*. Jul 15 2012;248(1-2):40-47.
27. Smolders J, Hupperts R, Barkhof F, et al. Efficacy of vitamin D3 as add-on therapy in patients with relapsing-remitting multiple sclerosis receiving subcutaneous interferon beta-1a: a Phase II, multicenter, double-blind, randomized, placebo-controlled trial. *Journal of the Neurological Sciences*. Dec 15 2011;311(1-2):44-49.
28. Torkildsen O, Grytten N, Aarseth J, Myhr KM, Kampman MT. Month of birth as a risk factor for multiple sclerosis: an update. *Acta Neurologica Scandinavica. Supplementum*. 2012(195):58-62.
29. Vukusic S, Confavreux C. Pregnancy and multiple sclerosis: the children of PRIMS. *Clinical Neurology and Neurosurgery*. Mar 2006;108(3):266-270.
30. Wingerchuk DM, Lesaux J, Rice GP, Kremenchutzky M, Ebers GC. A pilot study of oral calcitriol (1,25-dihydroxyvitamin D3) for relapsing-remitting multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry*. Sep 2005;76(9):1294-1296.
31. Wojcicki TR, Roberts SA, Learmonth YC, et al. Improving physical functional and quality of life in older adults with multiple sclerosis via a DVD-delivered exercise intervention: a study protocol. *BMJ Open*. 2014;4(12):e006250.
32. Yadav V, Bever C, Jr., Bowen J, et al. Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. Mar 25 2014;82(12):1083-1092.

## EXCLUDE: PARTICIPANTS

Excluded publications not reporting on participants with MS and risk factor studies excluding progressive MS:

1. Harandi AA, Shahbeigi S, Pakdaman H, Fereshtehnejad SM, Nikravesh E, Jalilzadeh R. Association of serum 25(OH) vitamin D3 concentration with severity of multiple sclerosis. *Iranian Journal of Neurology*. 2012;11(2):54-58.
2. Henderson VW. Alzheimer's disease and other neurological disorders. *Climacteric*. Oct 2007;10 Suppl 2:92-96.

## EXCLUDE: LANGUAGE

Excluded non-English language publications:

1. Ragonese P, Castiglia G, Cusimano V, Battaglieri F, Salemi G. Cigarette smoking, coffee consumption and multiple sclerosis risk: A case - Control study. *Acta Medica Mediterranea*. 2007;23(3):133-140.

## EXCLUDE: DUPLICATE

Duplicate publications:

1. Sandroff BM, Klaren RE, Pilutti LA, Dlugonski D, Benedict RHB, Motl RW. Randomized controlled trial of physical activity, cognition, and walking in multiple sclerosis. *Journal of Neurology*. Feb 2014;261(2):363-372.

# BACKGROUND

Reviews screened for additional references and multiple publications of included studies:


1. Multiple sclerosis - management of multiple sclerosis in primary and secondary care. October 2014.
2. Ascherio A. Environmental factors in multiple sclerosis. *Expert Review of Neurotherapeutics.* Dec 2013;13(12 Suppl):3-9.
3. Ascherio A, Munger K, White R, et al. Vitamin D as a predictor of multiple sclerosis activity and progression. *Mult. Scler. J.* Oct 2013;19(11):23-24.
4. Bowling AC, Stewart TM. Current Complementary and Alternative Therapies for Multiple Sclerosis. *Curr Treat Options Neurol.* Jan 2003;5(1):55-68.
5. Carrithers MD. Update on Disease-Modifying Treatments for Multiple Sclerosis. *Clinical Therapeutics.* Dec 1 2014;36(12):1938-1945.
6. Compston A, Coles A. Multiple sclerosis. *Lancet.* Apr 6 2002;359(9313):1221-1231.
7. Constantinescu C, Manouchehrinia A, Tench C, Bibani R, Britton J. Cigarette Smoking and Disease Progression in Patients with Multiple Sclerosis: A Study of a Large United Kingdom Cohort. *Neurology.* Apr 2012;78.
8. Dalgas U, Stenager E. Exercise and disease progression in multiple sclerosis: can exercise slow down the progression of multiple sclerosis? *Therapeutic Advances in Neurological Disorders.* Mar 2012;5(2):81-95.
9. Dalgas U, Stenager E, Sloth M, Stenager E. The effect of exercise on depressive symptoms in multiple sclerosis based on a meta-analysis and critical review of the literature. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies.* Mar 2015;22(3):443-e434.
10. D'Hooghe M B, Haentjens P, Nagels G, D'Hooghe T, De Keyser J. Menarche, oral contraceptives, pregnancy and progression of disability in relapsing onset and progressive onset multiple sclerosis. *Journal of Neurology.* May 2012;259(5):855-861.
11. D'Hooghe M B, Haentjens P, Nagels G, Garmyn M, De Keyser J. Sunlight exposure and sun sensitivity associated with disability progression in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2012;18(4):451-459.
12. D'Hooghe M B, Nagels G, Bissay V, De Keyser J. Modifiable factors influencing relapses and disability in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jul 2010;16(7):773-785.
13. D'Hooghe M B, Nagels G, De Keyser J, Haentjens P. Self-reported health promotion and disability progression in multiple sclerosis. *Journal of the Neurological Sciences.* Feb 15 2013;325(1-2):120-126.
14. Faridar A, Eskandari G, Sahraian MA, Minagar A, Azimi A. Vitamin D and multiple sclerosis: a critical review and recommendations on treatment. *Acta Neurol Belg.* Dec 2012;112(4):327-333.
15. Farinotti M, Vacchi L, Simi S, Di Pietrantonj C, Brait L, Filippini G. Dietary interventions for multiple sclerosis. *Cochrane Database Syst Rev.* 2012;12:CD004192.
16. Feinstein A, Dalgas U. The benefits of exercise in progressive MS: some cautious optimism. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Mar 2014;20(3):269-270.
17. Handel AE, Williamson AJ, Disanto G, Dobson R, Giovannoni G, Ramagopalan SV. Smoking and multiple sclerosis: an updated meta-analysis. *PloS One.* 2011;6(1):e16149.
18. Haselkorn JK. Veterans Health Administration Multiple Sclerosis Centers of Excellence: Clinical care, education, informatics, and research. *Journal of Rehabilitation Research and Development.* Jan-Feb 2006;43(1):vii-x.
19. Herndon RM. Medical hypothesis: why secondary progressive multiple sclerosis is a relentlessly progressive illness. *Archives of Neurology.* Feb 2002;59(2):301-304.
20. Hutchinson M. Multiparity in women with multiple sclerosis causes less long-term disability: Commentary. *Mult. Scler. J.* Oct 2014;20(11):1437-1438.
21. Jagannath VA, Fedorowicz Z, Asokan GV, Robak EW, Whamond L. Vitamin D for the management of multiple sclerosis. *Cochrane Database Syst Rev.* 2010(12):CD008422.
22. James E, Dobson R, Kuhle J, Baker D, Giovannoni G, Ramagopalan SV. The effect of vitamin D-related interventions on multiple sclerosis relapses: a meta-analysis. *Mult. Scler. J.* Oct 2013;19(12):1571-1579.
23. Kuhlmann T, Lingfeld G, Bitsch A, Schuchardt J, Bruck W. Acute axonal damage in multiple sclerosis is most extensive in early disease stages and decreases over time. *Brain: A Journal of Neurology.* Oct 2002;125(Pt 10):2202-2212.
24. Kurland LT, Molgaard CA, Kurland EM, Wiederholt WC, Kirkpatrick JW. Swine flu vaccine and multiple sclerosis. *JAMA.* May 25 1984;251(20):2672-2675.
25. Kurtzke JF. Clinical definition for multiple sclerosis treatment trials. *Annals of Neurology.* 1994;36

Suppl:S73-79.
26. Levin AB, Hadgkiss EJ, Weiland TJ, Jelinek GA. Meditation as an adjunct to the management of multiple sclerosis. *Neurology Research International.* 2014;2014:704691.
27. Levin AB, Hadgkiss EJ, Weiland TJ, et al. Can meditation influence quality of life, depression, and disease outcome in multiple sclerosis? Findings from a large international web-based study. *Behavioural Neurology.* 2014;2014:916519.
28. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* Jul 15 2014;83(3):278-286.
29. Manouchehrinia A, Weston M, Tench CR, Britton J, Constantinescu CS. Tobacco smoking and excess mortality in multiple sclerosis: a cohort study. *Journal of Neurology, Neurosurgery, and Psychiatry.* Oct 2014;85(10):1091-1095.
30. Marck CH, Hadgkiss EJ, Weiland TJ, van der Meer DM, Pereira NG, Jelinek GA. Physical activity and associated levels of disability and quality of life in people with multiple sclerosis: a large international survey. *BMC Neurol.* 2014;14:143.
31. Marrie RA, Cutter G, Tyry T. Substantial adverse association of visual and vascular comorbidities on visual disability in multiple sclerosis. *Mult. Scler. J.* Dec 2011;17(12):1464-1471.
32. Marrie RA, Hanwell H. General health issues in multiple sclerosis: comorbidities, secondary conditions, and health behaviors. *Continuum (Minneapolis, Minn.).* Aug 2013;19(4 Multiple Sclerosis):1046-1057.
33. Marrie RA, Horwitz RI. Emerging effects of comorbidities on multiple sclerosis. *The Lancet. Neurology.* Aug 2010;9(8):820-828.
34. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of Neurology.* Jul 2001;50(1):121-127.
35. Miller DH, Fazekas F, Montalban X, Reingold SC, Trojano M. Pregnancy, sex and hormonal factors in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2014;20(5):527-536.
36. Motl RW, McAuley E, Sandroff BM. Longitudinal change in physical activity and its correlates in relapsing-remitting multiple sclerosis. *Physical Therapy.* Aug 2013;93(8):1037-1048.
37. Octavia JR, Coninx K. Adaptive Personalized Training Games for Individual and Collaborative Rehabilitation of People with Multiple Sclerosis. *Biomed Res. Int.* 2014.
38. Overs S, Hughes CM, Haselkorn JK, Turner AP. Modifiable comorbidities and disability in multiple sclerosis. *Current Neurology and Neuroscience Reports.* Oct 2012;12(5):610-617.
39. Pilutti LA, Platta ME, Motl RW, Latimer-Cheung AE. The safety of exercise training in multiple sclerosis: A systematic review. *Journal of the Neurological Sciences.* Aug 2014;343(1-2):3-7.
40. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology.* Mar 1983;13(3):227-231.
41. Pozuelo-Moyano B, Benito-Leon J, Mitchell AJ, Hernandez-Gallego J. A systematic review of randomized, double-blind, placebo-controlled trials examining the clinical efficacy of vitamin D in multiple sclerosis. *Neuroepidemiology.* 2013;40(3):147-153.
42. Rezapour-Firouzi S, Arefhosseini SR, Mehdi F, et al. Immunomodulatory and therapeutic effects of Hot-nature diet and co-supplemented hemp seed, evening primrose oils intervention in multiple sclerosis patients. *Complementary Therapies in Medicine.* Oct 2013;21(5):473-480.
43. Rietberg MB, Brooks D, Uitdehaag BMJ, Kwakkel G. Exercise therapy for multiple sclerosis - art. no. CD003980.pub2. *Cochrane Database Syst Rev.* 2005(1).
44. Romberg A, Virtanen A, Ruutiainen J. Long-term exercise improves functional impairment but not quality of life in multiple sclerosis. *Journal of Neurology.* Jul 2005;252(7):839-845.
45. Sa MJ. Exercise therapy and multiple sclerosis: a systematic review. *Journal of Neurology.* Sep 2014;261(9):1651-1661.
46. Schwarz S, Leweling H. Multiple sclerosis and nutrition. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Feb 2005;11(1):24-32.
47. Simpson R, Booth J, Lawrence M, Byrne S, Mair F, Mercer S. Mindfulness based interventions in multiple sclerosis--a systematic review. *BMC Neurol.* 2014;14:15.
48. Stellmann JP, Neuhaus A, Lederer C, Daumer M, Heesen C. Validating predictors of disease progression in a large cohort of primary-progressive multiple sclerosis based on a systematic literature review. *PloS One.* 2014;9(3):e92761.
49. Swank RL. Multiple sclerosis: fat-oil relationship. *Nutrition.* Sep-Oct 1991;7(5):368-376.
50. Swank RL, Goodwin J. Review of MS patient survival on a Swank low saturated fat diet. *Nutrition.* Feb 2003;19(2):161-162.

51. Toomey E, Coote SB. Physical rehabilitation interventions in nonambulatory people with multiple sclerosis: a systematic review. *International Journal of Rehabilitation Research. Internationale Zeitschrift fur Rehabilitationsforschung. Revue Internationale de Recherches de Readaptation.* Dec 2012;35(4):281-291.
52. Tremlett HL, Devonshire VA. Does the season or month of birth influence disease progression in multiple sclerosis? *Neuroepidemiology.* 2006;26(4):195-198.
53. Vukusic S, Hutchinson M, Hours M, et al. Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. *Brain: A Journal of Neurology.* Jun 2004;127(Pt 6):1353-1360.
54. Wallin MT, Wilken JA, Turner AP, Williams RM, Kane R. Depression and multiple sclerosis: Review of a lethal combination. *Journal of Rehabilitation Research and Development.* Jan-Feb 2006;43(1):45-62.
55. Wergeland S, Torkildsen O, Bo L, Myhr KM. Polyunsaturated fatty acids in multiple sclerosis therapy. *Acta Neurologica Scandinavica.* Dec 2012;126:70-75.
56. Wier LM, Hatcher MS, Triche EW, Lo AC. Effect of robot-assisted versus conventional body-weight-supported treadmill training on quality of life for people with multiple sclerosis. *Journal of Rehabilitation Research and Development.* 2011;48(4):483-492.
57. Wingerchuk DM. Smoking: effects on multiple sclerosis susceptibility and disease progression. *Ther Adv Neurol Disord.* Jan 2012;5(1):13-22.
58. Yeh EA, Weinstock-Guttman B. Multiple sclerosis: predicting risk and delaying progression. *The Lancet. Neurology.* Jan 2010;9(1):7-9.

# APPENDIX C. CRITERIA USED IN QUALITY ASSESSMENT

This appendix documents the individual risk of bias criteria used to assess included studies. In addition, it documents the criteria used to rate the quality of evidence across studies.

## RISK OF BIAS ASSESSMENT OF KQ1 AND KQ2 STUDIES

A large number of diverse studies contributed to the review. We broadly categorized risk factor studies into concurrent, retrospective, and prospective studies. Concurrent and retrospective studies can provide only limited information on questions of progression, regardless of their methodological quality, and these studies were not further differentiated.

The identified prospective studies relevant to KQ1 and KQ2 were assessed with QUIPS (QUality In Prognosis Studies), a critical appraisal tool for prognostic studies. QUIPS assesses the domains study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.[15] For each domain we determined whether the study indicates high risk of bias, moderate risk of bias, or low risk of bias.

**Appendix Table 1. Risk of Bias: KQ1 and KQ2 Prospective Studies**

| Author, year | Study Participation | Study Attrition | Prognostic Factor Measurement | Outcome Measurement | Study Confounding | Statistical Analysis and Reporting | KQ1 and KQ2 |
|---|---|---|---|---|---|---|---|
| Ascherio, 2014[20] | High | Moderate | Low | Low | Moderate | Low | |
| Confavreux, 1998[30] | Low | Low | Low | Low | High | Low | |
| Detels, 1982[35] | Low | Moderate | Moderate | High | Moderate | Moderate | |
| Mowry, 2012[69] | Low | Low | Low | Low | Low | Low | |
| Pasto, 2012[72] | Low | Low | Low | Low | High | Low | |
| Pittas, 2009[76] | Moderate | Low | Low | Low | Low | Low | |
| Runmarker, 1995[113] | Moderate | Low | Low | Low | High | Moderate | |
| Shammas, 2014[87] | High | Low | Low | Low | Moderate | High | |
| Soilu-Hanninen, 2007[91] | High | Low | Low | Low | Moderate | High | |
| Stuifbergen, 2006[96] | Low | Low | Low | Low | Low | Low | |
| Sundstom, 2008[97] | Moderate | Low | Moderate | Low | Low | Moderate | |
| Swank, 1990[98] | Low | Low | High | Low | Low | Moderate | |
| Tepavcevic, 2010[112] | Moderate | Moderate | High | Low | Moderate | High | |

**Legend:**

**Study participation**: Prompting items: a. Adequate participation in the study by eligible persons, b. Description of the source population or population of interest, c. Description of the baseline study sample, d. Adequate description of the sampling frame, and recruitment, e. Adequate description of the period and place of recruitment, f. Adequate description of inclusion and exclusion criteria. Ratings: High risk: The relationship between the PF and outcome is very likely to be different for participants and eligible nonparticipants; Moderate bias: The relationship between the PF and outcome may be different for participants and eligible nonparticipants; Low bias: The relationship between the PF and outcome is unlikely to be different for participants and eligible nonparticipants

**Study attrition**: a. Adequate response rate for study participants, b. Description of attempts to collect information on participants who dropped out, c. Reasons for loss to follow-up are provided, d. Adequate description of participants lost to follow-up, e. There are no important differences between participants who completed the study and those who did not. Ratings: High bias: The relationship between the PF and outcome is very likely to be different for completing and non-completing participants; Moderate bias: The relationship between the PF and outcome may be different for completing and non-completing participants; Low bias: The relationship between the PF and outcome is unlikely to be different for completing and non-completing participants

**Prognostic Factor Measurement**: Prompting items: a. A clear definition or description of the PF is provided, b. Method of PF measurement is adequately valid and reliable, c. Continuous variables are reported or appropriate cut points are used, d. The method and setting of measurement of PF is the same for all study participants, e. Adequate proportion of the study sample has complete data for the PF, f. Appropriate methods of imputation are used for missing PF data. Ratings: High bias: The measurement of the PF is very likely to be different for different levels of the outcome of interest, Moderate bias: The measurement of the PF may be different for different levels of the outcome of interest, Low bias: The measurement of the PF is unlikely to be different for different levels of the outcome of interest

**Outcome Measurement**: Prompting items: a. clear definition of the outcome is provided, b. Method of outcome measurement used is adequately valid and reliable, c. The method and setting of outcome measurement is the same for all study participants. Ratings: High bias: The measurement of the outcome is very likely to be different related to the baseline level of the PF, Moderate bias: The measurement of the outcome may be different related to the baseline level of the PF, Low bias: The measurement of the outcome is unlikely to be different related to the baseline level of the PF

**Study Confounding**: Prompting items: a. All important confounders are measured, b. Clear definitions of the important confounders measured are provided, c. Measurement of all important confounders is adequately valid and reliable, d. The method and setting of confounding measurement are the same for all study participants, e. Appropriate methods are used if imputation is used for missing confounder data, f. Important potential confounders are accounted for in the study design, g. Important potential confounders are accounted for in the analysis. Ratings: High bias: The observed effect of the PF on the outcome is very likely to be distorted by another factor related to PF and outcome, Moderate bias: The observed effect of the PF on outcome may be distorted by another factor related to PF and outcome, Low bias: The observed effect of the PF on outcome is unlikely to be distorted by another factor related to PF and outcome

**Statistical Analysis and Reporting**: Prompting items: a. Sufficient presentation of data to assess the adequacy of the analytic strategy, b. Strategy for model building is appropriate and is based on a conceptual framework or model, c. The selected statistical model is adequate for the design of the study, d. There is no selective reporting of results. Ratings: High bias: The reported results are very likely to be spurious or biased related to analysis or reporting, Moderate bias: The reported results may be spurious or biased related to analysis or reporting, Low bias: The reported results are unlikely to be spurious or biased related to analysis or reporting

## RISK OF BIAS ASSESSMENT OF KQ3 STUDIES

Studies relevant to KQ3 were assessed with the Cochrane risk of bias tool. The tool assesses random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessors (detection bias), completeness of reporting outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias (if appropriate) for each of the included studies. For each domain

we determined whether the study indicates a high risk of bias, a low risk of bias, or an unclear risk of bias.

**Appendix Table 2. Risk of Bias: KQ3 Studies**

| Author, year | Random sequence generation | Allocation concealment | Blinding of participants/ providers | Blinding of outcome assessors | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| Armutlu, 2001[19] | Unclear | Unclear | High risk | Low risk | Low risk | Low risk | Low risk |
| Bates, 1977[24] | Unclear | Unclear | Low risk | Low risk | Low risk | High risk | Low risk |
| Bates, 1978[25] | Unclear | Unclear | Low risk | Low risk | Unclear | Unclear | Unclear |
| Bates, 1989[23] | Unclear | Unclear | Low risk | Low risk | Unclear | Unclear | Unclear |
| Bjarnadottir, 2007[26] | Unclear | Low risk | High risk | High risk | Unclear | Unclear | High risk |
| Burton, 2010[28] | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk |
| Carter, 2013[29] | Low risk | Low risk | High risk | Low risk | Low risk | Low risk | Low risk |
| Conklyn, 2010[31] | Unclear | Unclear | High risk | High risk | Low risk | Low risk | High risk |
| Dalgas, 2009[32] | Unclear | Low risk | High risk | Low risk | Low risk | Low risk | Low risk |
| DeBolt, 2004[34] | Unclear | Unclear | High risk | High risk | Unclear | Unclear | Unclear |
| Fimland, 2010[37] | Unclear | Unclear | Unclear | Unclear | Low risk | Low risk | High risk |
| Golzari, 2010[42] | Unclear | Unclear | High risk | Low risk | Unclear | Unclear | High risk |
| Harbige, 2007[44] | Unclear | Unclear | Low risk | Low risk | Unclear | Unclear | High risk |
| Kampman, 2012[49] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Lo, 2008[56] | Unclear | Unclear | High risk | Low risk | Low risk | Low risk | High risk |
| Millar, 1973[65] | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk |
| Miller, 2011[66] | Unclear | Unclear | High risk | Unclear | Low risk | Low risk | Unclear |
| Mosayebi, 2011[67] | Unclear | Low risk | Low risk | Low risk | High risk | Low risk | Unclear |
| Pantzaris, 2013[71] | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Paty, 1978[73] | Unclear | Unclear | Low risk | Low risk | High risk | Unclear | Unclear |
| Petajan, 1996[74] | Unclear | Unclear | High risk | Low risk | High risk | Low risk | High risk |
| Pfalzer, 2011[75] | Unclear | Unclear | High risk | Unclear | Unclear | Low risk | Low risk |
| Ramirez-Ramirez, 2013[78] | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk |
| Rampello, 2007[79] | Low risk | Low risk | Unclear | Unclear | High risk | Unclear | Unclear |
| Rezapour-Firouzi, 2013[80] | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | High risk |
| Romberg, 2004[81] | Unclear | Unclear | High risk | High risk | Low risk | Unclear | Unclear |
| Sangelaji, 2014[83] | Unclear | Low risk | High risk | Unclear | High risk | Low risk | Low risk |
| Schwartz, 2012[84] | Low risk | Low risk | High risk | Low risk | High risk | Low risk | High risk |
| Shaygannejad, 2012[88] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Soilu-Hanninen, 2012[128] | Low risk | Low risk | Low risk | Low risk | High risk | Unclear | High risk |
| Solari, 1999[92] | Low risk | Low risk | High risk | Low risk | Low risk | Low risk | Low risk |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Stein, 2011[94] | Low risk | Low risk | High risk | Low risk | Low risk | High risk | High risk |
| Torkildsen, 2012[101] | Low risk | Low risk | Low risk | Low risk | Unclear | Low risk | Unclear |
| Weinstock-Guttman, 2005[107] | Unclear | Unclear | Low risk | Low risk | High risk | Low risk | High risk |
| Wiles, 2001[109] | Unclear | Unclear | High risk | Low risk | Low risk | Low risk | Low risk |
| Yadav, 2014[110] | Unclear | Unclear | High risk | Low risk | High risk | Low risk | High risk |

**Legend:**

**Random sequence generation**: Low risk: The investigators describe a random component in the sequence generation process such as: Referring to a random number table, Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization; High risk: The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: Sequence generated by odd or even date of birth; Sequence generated by some rule based on date (or day) of admission; Sequence generated by some rule based on hospital or clinic record number; Allocation by judgment of the clinician; Allocation by preference of the participant; Allocation based on the results of a laboratory test or a series of tests; Allocation by availability of the intervention. Unclear: Insufficient information about the sequence generation process to permit judgment of 'Low risk' or 'High risk'.

**Allocation concealment**: Low risk: Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: Central allocation (including telephone, web-based and pharmacy-controlled randomization); Sequentially numbered drug containers of identical appearance; Sequentially numbered, opaque, sealed envelopes. High risk: Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: Using an open random allocation schedule (*eg*, a list of random numbers); Assignment envelopes were used without appropriate safeguards (*eg*, if envelopes were unsealed or non-opaque or not sequentially numbered); Alternation or rotation; Date of birth; Case record number; Any other explicitly unconcealed procedure. Unclear: Insufficient information to permit judgment of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

**Blinding of participants and personnel**: Low risk: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. High risk: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. Unclear: Insufficient information to permit judgment of 'Low risk' or 'High risk'; The study did not address this outcome.

**Blinding of outcome assessment**: Low risk: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. High risk: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding. Unclear: Insufficient information to permit judgment of 'Low risk' or 'High risk'; The study did not address this outcome.

**Incomplete outcome data**: Low risk: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods. High risk:

Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; Potentially inappropriate application of simple imputation. Unclear: Insufficient reporting of attrition/exclusions to permit judgment of 'Low risk' or 'High risk' (*eg*, number randomized not stated, no reasons for missing data provided); The study did not address this outcome.

**Selective reporting**: Low risk: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon). High risk: Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (*eg*, subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study. Unclear: Insufficient information to permit judgment of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.

**Other bias**: Low risk: The study appears to be free of other sources of bias. High risk: There is at least one important risk of bias. For example the study had a potential source of bias related to the specific study design used; has been claimed to have been fraudulent; or had some other problem. Unclear: There may be a risk of bias, but there is either: Insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.

## CRITERIA TO RATE THE BODY OF EVIDENCE FOR KQ1 AND KQ2

The GRADE framework for prognostic factor research[18] differentiates 8 criteria that are used to evaluate the quality of the evidence across all identified studies:

The *phase of investigation* differentiates whether the risk factor evidence is primarily based on a study that aimed to identify potential prognostic factors (moderate quality) rather than based on studies aiming to confirm identified associations or explanatory research aiming to understand prognostic pathways (high quality).

*Study limitations* took the assessment frame into account by differentiating whether the risk factor status and the outcome variable were assessed at the same time (concurrently), retrospectively, or prospectively. Prospective studies were further differentiated by the risk of bias based on the QUIPS scores.

*Inconsistency* assessed whether the identified association was consistently present across studies and across study designs (*eg*, present in concurrent and prospective studies).

*Indirectness* took into account whether the available research studies does not accurately reflect the review question. Examples are cases where the only available research studies reported on vitamin D status, rather than a directly patient-modifiable risk factor such as vitamin D intake.

Evidence was downgraded for *imprecision* if the sample size was insufficient, the confidence interval was wide and overlapped the value of no effect, there were less than 10 outcome events for each prognostic variable, or there were less than 100 cases reaching endpoints.

Evidence was downgraded for *publication bias* unless the value of the risk or protective factor in predicting the outcome has been repetitively investigated.

Evidence for individual risk factors may be upgraded if *effects* are moderate or large or there is evidence of *exposure-gradient* response for factors measured at different doses.

## CRITERIA TO RATE THE BODY OF EVIDENCE FOR KQ3

For KQ3 we took the criteria *risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect, dose response,* and *all plausible residual confounding would reduce a demonstrated effect and/or would suggest a spurious effect if no effect was observed* into account. The starting point was high evidence because the data are based on RCTs.

Risk of bias, inconsistency, indirectness, imprecision, and publication bias can lower the quality. Large effect, dose response, and all plausible residual confounding can upgrade the quality of the body of evidence. [17]

*Risk of bias* evaluations were based on the above documented Cochrane Risk of Bias tool assessments. *Inconsistency* took the direction and the size of effects across studies into account. *Indirectness* may assess whether comparative effects are based on head-to-head trial evidence or was obtained from meta-regressions and subgroup analyses. *Imprecision* takes the confidence interval around the point estimate into account. *Publication bias* was assessed to determine whether there is evidence that pertinent studies, in this case negative effect studies are missing.

# APPENDIX D. PEER REVIEW COMMENTS/AUTHOR RESPONSES

| Comment | Response |
|---|---|
| Studies missing - Yes - Studies evaluating geography itself as a risk factor, studies prior to 1973, studies involving co-morbidity | The identified studies on associations between geography and progression are shown in the “other” and the “multiple” risk factor section.<br>Studies published prior to 1973 were eligible for inclusion in the review and all databases were searched without date restriction. We have added the eligibility criteria after the description of the included studies in the result section to avoid ambiguity. In addition, we have emphasized that databases were searched from inception.<br>Co-morbidities were outside the scope of this review but we have expanded the future research section to indicate that sufficient literature exists for systematic reviews on several individual co-morbidities. |
| It would have been useful to add obesity related studies in the review as it appears to be an important co-morbid condition and related information would have been of great research as well as clinical significance. | See above. In particular there is a growing literature on weight and MS progression; we have expanded on this issue in the future research section. |
| Several typographical errors are present in the draft, that I assume will be reviewed carefully towards the final draft. | Typographical errors will be correct before publication |
| Pg 1/Line 8: Traumatic brain injury is more common than MS in younger adults but is not progressive. I’d reword this sentence as follows: Multiple sclerosis (MS) is the most common progressive disease of the central nervous system in young adults and the cause of serious physical disability in adults of working age. | Revised as suggested |
| Pg 1/Line 21: Use “MS” throughout the manuscript after it’s defined. | We have revised the text accordingly but left the key questions as is to avoid ambiguity |
| Pg 1/Line 49: Is this a preliminary report vs. final? | The draft report is subjected to peer review |
| Pg 3/Line 16: “Concurrent” is not commonly used and is confusing. It should be replaced with retrospective. | To address this point, we have added a definition to avoid confusion (measuring the exposure status and the outcome at the same time point, *eg*, current alcohol intake) |
| Pg 5/Line 5: Change “Out” to Our. | Changed |
| Pg 5/Line 25: There are several redundant and inaccurate statements in the conclusion. The association between MS progression and vitamin D supplementation is not significant but the conclusions imply it is related. The conclusion should be modified to something like the following:<br>Our systematic review documents the available evidence on modifiable risk factors for MS progression. Associations with MS progression are strongest for smoking. None of the intervention studies examining exercise, dietary, and vitamin D supplementation reported a statistically significant effect on MS disability. Other than smoking cessation, there are no other modifiable risk factors that can be given support from this review as an intervention worthy of slowing MS progression. | To address the perceived redundancy we have divided the conclusions into multiple paragraphs: one characterizes the overall evidence base, one summarizes the risk factor studies, one summarizes the intervention RCTs, and the last one describes the evidence for factors that were addressed in both, risk factor and in intervention studies. The correlation between EDSS scores and vitamin D level was statistically significant. We have revised the sentence to avoid the perceived inaccuracy. |

| | |
|---|---|
| Pg 8/Line 3: There are several reviews of MS risk factors published in the literature. Some are comprehensive in scope. The statement below is confusing in implying there are multiple reviews of risk factors translated into treatment options. Is this referring to dietary or exercise treatments?<br>There is an emerging body of research that evaluates risk factors translated into treatment options but no systematic review has to date comprehensively synthesized the available evidence. | We have deleted the sentence |
| Pg 18/Line 8: Why was 1973 used as the starting year (vs. 1970)? | See above |
| Pg 51/Line 5: There is no figure in the box. | Unfortunately the conversion to PDF in the online editorial manager system did not display the figure; this will be corrected in the final report. |
| Forest plots: There is no confidence interval represented on the summary measure of risk in the diagram. This should be included. | We were not sure how this perception came about, confidence intervals are shown for individual studies and the pooled effect in all forest plots |
| Please see editorial suggestions and comments in the uploaded document. | Thank you for your careful review; we have accepted all editorial changes |
| p. 10: So if I understand correctly, a study on solely Relapsing Remitting MS (RR MS), the most common disease type, would have been excluded - even though patients with RR MS often progress over time? | We have revised the sentence to avoid confusion |
| p. 24: Sentence is unclear. Which of the studies does this phrase refer to? | Author name added to avoid ambiguity |
| p. 50: awkward wording | Revised to clarify that the individually assessed risk factors as well as predicted outcomes were very specific |
| p. 51: Figure missing from draft | See above |
| p. 51: I assume you mean since the Vit D values were dichotomized, rather than reported as a continuous variable? The statement is unclear as written, since the study did in fact use the EDSS. | The studies did not report on a correlation, hence they could not be added to the meta-analysis; we have clarified this in the text |
| p. 52: Graphs have a diagonal line, which should be deleted. | Formatting changes are due to converting to PDF and will be corrected in the final report |
| p. 54: Which - any alcohol consumption, or heavy drinking, or both? | Clarified |
| p. 56: Explain the "downgrades" (or refer to the text in the legend) | Added |
| p. 69: Unclear in this context | We have added more explanation regarding the waitlist condition |
| p. 78: Would this be better expressed as "pregnancy" rather than "children"? | See above |
| p. 82: Unclear. Do you mean "for which the published evidence demonstrates their amenability...". Need a clear statement to conclude the review! | We have revised the draft conclusions |
| Did any study examine the impact of moving to a different region/climate/latitude during childhood or early adulthood? | We did not identify such a study |
| I have a general concern that there may be confusion in discussion of studies between change from Relapsing-Remitting MS (RR MS) to Secondary Progressive MS (SP MS), and progression of disability caused by MS, which can occur both in RR MS and SP MS. | Yes, several studies did not restrict to RR MS and studies used a variety of outcome measures. To address this concern, we have highlighted those studies in the summary of findings section that specifically reported on the change from RR to SP MS and those that only included patients with RR MS at baseline |

| | |
|---|---|
| Was the post-partum period also analyzed separate from pregnancy itself? It is commonly held that MS is likely to be quiescent during pregnancy, but the risk for relapses or progression is increased from baseline during the immediate post-partum interval. | Given the complexity of the topic and the diversity across the large number of studies that should be addressed in a separate systematic review we have added this topic to the list of suggested future research studies. |
| Page 5, line 5: Change "Out" to "Our" | See above |
| Page 7, line 16: Change "described" to "characterized pathologically" and add "focal areas of" before "inflammation..." | Changed as suggested |
| Page 7, lines 35 to 37: Change "Progressive relapsing MS" to "Active progressive MS" The classification system for MS subtypes was revised in 2014 to remove the classification of "progressive relapsing" and replace it with the classification of "active progressive" This is given in Reference 8. | Changed as suggested |
| Page 10, line 60: Azathioprine is listed as a medication specifically designed for MS, which . Azathioprine was originally developed as an antineoplastic agent it is now used for immunosuppression in autoimmune diseases and organ transplantation. Other drugs in this class that were omitted from the list include methotrexate and cyclophosphamide. Cladribine, listed later, probably belongs in the same list. | We have removed the specific examples and reduced the text to one example per medication type to address this point |
| Page 13, line 54: Move "presented" to after "statistics" | We have revised the sentence |
| Page 15, line 14: After "East" add ", Professor, Departments of Neurology, Pharmacology and Physical Therapy, University of Maryland School of Medicine" | Added |
| Page 15, line 14: After "MPH" add ", Director, MS Center of Excellence - West" | Added |
| Page 15, line 26: Change,"PHD" to "PhD" | Changed |
| Tables 1 to 7: I may not be reading the tables correctly but I did not see a column indicating the rating of the quality of the evidence in each study. I believe that Appendix C deals with that issue in detail but should some summary indication be included on these tables? | The studies were assessed with a number of individual risk of bias criteria which exceeded the available space in the evidence tables. To address this point we have systematically added information on the risk of bias to the result sections following the evidence tables |
| Tables 1 to 7, case definition: I may not be understanding what is being reported here. I am used to this column being used to report whether an acceptable case definition was used by the study in question. In most cases this would involve a diagnosis of MS based on published criteria such as the Poser, McDonald or modified McDonald criteria. Cases might be further restricted based on disability range using a scale like the EDSS score. The entries in this column don't seem to fit this so I am unclear on what is being displayed here. I am also not clear on whether publications were reviewed to ensure that accepted case definitions were used. | We have revised the term to “predicted variable” to avoid confusion with MS diagnostic criteria. In addition, we have added the diagnostic criteria for prospective studies to the evidence tables. |