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The role of lifestyle physical activity in preventing multiple sclerosis

review paper
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ABSTRACT
Multiple sclerosis (MS) is a devastating neurodegenerative disorder that affects more than three million people worldwide. Among the environmental, lifestyle, dietary, comorbid, and pharmacological factors investigated as possible modifiable protective or risk factors for MS, physical activity (PA) seems to play a valuable role in its prevention. Currently, there is no comprehensive review article on the preventive effects of PA in MS. This narrative review aimed to evaluate the most recent and extensive pooled analysis and evidence and to explore the influence of lifestyle PA on primary and secondary prevention in MS. Literature articles were searched through several databases, including PubMed, Cochrane Library, Embase, and Web of Science, from 1985 to March 2024. The review focused on lifestyle PA, defined as the daily accumulation of at least 30 min of self-selected activities. This includes all leisure, occupational, or household activities that are at least moderate to vigorous in intensity and may be planned or unplanned activities that are part of everyday life. The most valuable and representative reports on primary and secondary prevention in MS have been selected. Lifestyle PA, practised at moderate and high intensity, plays a protective role in reducing the risk of developing MS and delaying the onset of disability in persons with MS. Future studies are required to identify specific types of PA that are particularly recommended for patients with MS.
Key words: prevention, physical activity, MS, disability, multiple sclerosis

Introduction

Multiple sclerosis (MS) is a devastating neurodegenerative disorder that affects the brain and spinal cord, slowly robbing patients of their physical mobility, vision, and balance. According to Walton et al. [1], the global prevalence of MS has risen since 2013 and reached 2.8 million in 2020, which translates to 35.9 per 100,000 population. The pooled incidence rate across 75 reporting countries was 2.1 per 100,000 persons/year, and the mean age of diagnosis was 32 years; females are twice as likely to live with MS as males [1]. The symptoms of multifocal damage (demyelination and axonal breakdown) of nervous tissue lead to inevitable disability.

Many studies have suggested an association between physical activity (PA) and the risk of MS, as well as its role in slowing disability. PA, exercise, and physical fitness are usually considered to refer to the same phenomenon and are used interchangeably, but they have different meanings. The WHO continues to use the unclear definition of PA proposed by Caspersen et al. in 1985, which describes it as "any body movement produced by skeletal muscles that leads to the expenditure of energy." Exercise was classified by these authors as a subset of PA consisting of planned, structured, and repeatable activities whose ultimate or intermediate goal is to improve or maintain physical fitness, understood as a set of attributes related to health and skills that can be measured using specific tests [2]. PA in everyday life takes different forms, determined by where it is undertaken (workplace, home) and its purpose (sport, physical conditioning). According to Strath et al. [3], who presented a guide to the assessment of PA on behalf of the American Heart Association (AHA), it has four dimensions: (1) method or type, (2) frequency (every day, several times a week), (3) duration (e.g., 15 min, 30 min, 45 min, 60 min, 90 min), and (4) intensity (low, moderate, high).

In the scientific statement of the AHA presented by Fletcher et al. [4], physical exercise was classified into relatively intense (based on the maximum heart

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rate calculated from the table for age) and intense [based on the metabolic equivalent of the task (MET; one MET is defined as the amount of O_2 that a person consumes at rest, calculated as 3.5 ml O_2/kg body weight/min, or 1 kcal/kg/h, or 4.184 kJ/kg/h)]. For illustration, moderate exercise intensity involves 50–69% of maximum heart rate and a MET of 3.0–5.9, whereas severe exercise intensity occurs at 70–89% of maximum heart rate and above a MET of 6. In everyday terms, eating a meal has a MET of 1–1.5, and taking a shower has a MET of 3–3.5 [4].

The group of experts from the National MS Society provided definitions of PA and lifestyle PA [5]. According to Bouchard and Shephard [6], "PA, including lifestyle PA and exercise, comprises any bodily movement produced by skeletal muscle contraction that results in a substantial increase in energy expenditure over resting levels." Following Dunn et al. [7], lifestyle PA is the daily accumulation of at least 30 min of self-selected activities, which includes all leisure, occupational, or household activities that are at least moderate to vigorous in their intensity and could be planned or unplanned activities that are part of everyday life.

The following two sections contain the narrative review on the importance of lifestyle PA in the primary prevention of MS and as secondary prevention in delaying disability.

The importance of PA in primary prevention of MS

Hillman et al. [8], based on literature, found evidence of the positive neuroprotective effects of aerobic PA on cognition and brain function, at the molecular, cellular, systems, and behavioral levels through adaptive neuroplasticity. A growing number of studies support the idea that physical exercise is a lifestyle factor that might lead to increased physical and mental health throughout life [8].

Despite widespread knowledge about the beneficial effects of PA in the prevention and treatment of many diseases, low activity in patients is still observed. This also applies to patients with MS, whose PA is lower than that of the general population. Cross-sectional research conducted among 145,000 inhabitants of Hordaland County, Norway, in 1997 (including 87 patients with MS) showed that patients with MS had a high rate of cigarette smoking, a low average BMI, and a lower level of PA compared to the rest of the study population [9]. In 2005, Motl et al. [10] conducted a meta-analysis of 13 studies involving 2,360 participants with MS. Higher PA was found in healthy people compared to the sick population, and higher PA was observed in primary progressive multiple sclerosis than in relapsing remitting multiple sclerosis (RRMS).

Ng and Kent-Braun [11] tested the hypothesis that PA was lower in a group of 17 MS patients (mean ± *SD*; age = 46 ± 6 years, 11 females, 6 males) compared with 15 healthy sedentary control subjects (age = 44 ± 7 years, 9 females, 6 males). PA was measured with a three-dimensional accelerometer and an activity questionnaire for 7 days. Vector magnitude values from the accelerometer for the MS and sedentary control subjects were 121,027 ± 59,336 and 185,892 ± 60,566 arbitrary units/day, respectively ($p = 0.01$). Estimated energy expenditure values derived from the questionnaire were 35.9 ± 3.0 and 36.2 ± 4.1 kcal/kg/day (NS), respectively. Thus, when measured directly with an accelerometer, activity was lower in MS compared with sedentary control subjects [11].

In an editorial published in 2022 in *Frontiers in Neurology*, Dobson et al. [12] stated that MS prevention has been identified as a key aim across MS research. The problem is that there is a long lag between many identified risk factors and clinical MS development, and many people exposed to these risk factors never develop MS. It is clear that MS has a complex pathogenic pathway with contributions from and interactions between genes and the environment. The authors presented a group of papers exploring opportunities and challenges around MS prevention and how some of these challenges may be overcome. Though MS cannot be completely prevented, quitting smoking (if applicable), maintaining moderate body weight (especially in childhood), and getting enough vitamin D through diet or sun exposure could help reduce the risk [12].

The number of reports on the effects of PA in the primary prevention of MS is relatively low. Frau et al. [13] evaluated the attitudes toward PA of a group of MS patients and the differences in PA practice before and after diagnosis. Out of 118 patients, 37% practised PA only before the diagnosis, 9% only after, and 52% during both periods. After the diagnosis, 64% of participants noted some negative differences in PA, particularly less physical resistance and worsening of symptoms, and 38% stopped PA. However, patients reported benefits from PA when they resumed activity after diagnosis. Individual exercises rather than group activities were preferred after diagnosis. Only 26% of patients knew that adapted PA existed and understood the differences between adapted PA and classic physiotherapy. The authors observed a reduction in PA practice among patients who started their activity after the diagnosis of MS, but active patients reported benefits from PA [13].

Dorans et al. [14] studied PA during adulthood or early life in association with MS incidence in two prospective cohorts of women. Women in the Nurses' Health Study (NHS) (n = 81,723; 1986–2004) and NHS II (n = 111,804; 1989–2009) reported recent PA at baseline and in selected follow-up questionnaires. There were 341 confirmed MS cases with first symptoms after baseline. Participants also reported early-life activity. Compared with women in the lowest baseline PA quartile, women in the highest quartile had a 27% reduced rate of MS; this trend was not present in 6-year lagged analyses. Changes in PA suggested that women reduced activity before the onset of MS symptoms. In NHS and NHS II, higher strenuous activity at ages 18–22 years was weakly associated with a decreased MS rate. However, in NHS II, total early-life activity at ages 12–22 was not associated with MS [14].

Wesnes et al. [15] studied 1,904 MS cases and 3,694 controls and found that vigorous PA was inversely associated with the risk of MS (OR = 0.74, 95% CI: 0.63–0.87, $p < 0.001$), suggesting the potential protective role of PA against MS. Li et al. [16] estimated genetic correlations in MS and then conducted two-sample and multivariable Mendelian randomization analyses based on summary statistics from previous large genome-wide association studies. A significant genetic correlation was identified between moderate PA and the risk of MS (genetic correlation: –0.15, SE = 0.05, p = 0.0029). Meanwhile, higher moderate PA was significantly associated with a reduced risk of MS. This association was further verified using summary statistics from another study on overall PA. These results suggest that moderate PA could reduce the risk of MS. These findings help better understand the role of PA in MS and provide some lifestyle recommendations for individuals susceptible to MS [16].

The role of PA in secondary prevention of disability in MS

The leading role in research on PA in MS is played by the team from the Department of Kinesiology and Community Health at the University of Illinois at Urbana-Champaign, led by Professor Robert Motl. Sandroff et al. [17] compared PA between two equal-sized groups of 77 people with MS and a control group matched for age, height, weight, and sex. Statistically significant differences were found between groups in the accelerometric assessment of activity, including the number of steps, time spent in moderate to intense PA, results on the Godin Questionnaire (GLTEQ), and on the International Physical Activity Questionnaire – Short Form (IPAQ). The mean score of these scales showed that people with MS were generally moderately less physically active than the control group. Conclusions: the main finding was a moderate reduction in PA among people with MS, but its magnitude was much smaller than reported in a previously published meta-analysis [17].

Motl et al. [18], in a cross-sectional observational study, included 49 persons with MS. Participants wore an accelerometer around the waist during waking hours for a 7-day period to measure PA and sedentary behaviours and completed a maximal incremental exercise test on an electronically-braked, computer-controlled cycle ergometer with open-circuit spirometry to measure peak aerobic capacity (VO_2peak). Results: VO_2peak was significantly correlated with moderate to vigorous PA (MVPA) ($r = 0.53$, $p < 0.001$) and leisure-time physical activity (LPA) ($r = 0.39$, $p < 0.01$), but not sedentary behaviour ($r = -0.12$, $p = 0.44$). The authors concluded that they provided the first evidence that MVPA and LPA represent concurrent correlates of VO_2peak and both could be targeted for improving aerobic capacity in persons with MS [18].

A systematic review of correlates and determinants of PA in persons with MS from 1980 to 2015 comprised 56 publications with data from observational studies and 2 interventional studies, providing evidence for 86 different variables. Consistent correlates of PA were the disability level, walking limitations in particular, PA-related self-efficacy, self-regulation constructs, employment status, and educational level. Fifty-nine of the 86 investigated variables in observational studies are based on one or two study findings. Besides the importance of the general disability level and walking limitations, the results highlighted the importance of personal factors (e.g., PA-related self-efficacy, self-regulatory constructs, sociodemographic factors) [19].

Arntzen et al. [20] reviewed the effect of exercise and PA interventions on step count and intensity level in individuals with MS. A total of eight randomized clinical trials involving 919 individuals with MS (77.8% women) were included. The results of this meta-analysis showed no significant differences in step count and MVPA levels among individuals with MS, both within and between groups receiving PA interventions [20].

Gervasoni et al. [21] published the results of a multicenter cross-sectional study on PA in non-disabled people with early MS (PwMS). They assessed 58 PwMS (39.1 ± 10.6 years) and 20 healthy persons (39.3 ± 8.9 years). Subjects wore the wrist GENEActiv accelerometer for 7 days. The authors concluded that the PA level of PwMS differs from that of healthy subjects, even in early diagnosed subjects. In PwMS with Expanded Disability Status Scale (EDSS) 0–1.5 only, fatigue is associated with prolonged inactive behavior. Conversely, in PwMS with EDSS 2–2.5, both inactivity and vigorous activities are modulated by fatigue and endurance and are associated with different levels of social participation [21].

Pedullà et al. [22] developed and disseminated an international online survey between December 2020 and July 2021, investigating changes in self-reported PA type, duration, frequency, and intensity due to the COVID-19 outbreak in PwMS with differing disability levels. Among respondents (n = 3,810), 3,725 were eligible. The proportion of those who conducted at least one activity decreased with increasing disability levels at both time points (pre and during). Overall, 60% of respondents met the international guidelines referring to PA before the pandemic, with a reduction of approximately 10% occurring during the pandemic in all disability groups. Respondents with higher disability participated more in physical therapy and less in walking, cycling, and running at both time points. Most respondents reported practising PA at a moderate intensity at both time points; frequency and duration of sessions decreased as disability level increased [22].

Recently, Wanitschek et al. [23] published the results of a cross-sectional study on patient-reported outcomes of PA and accelerometry in people with MS and ambulatory impairment. A total of 56 pwMS completed the study, with a mean (SD) age of 48.4 (10.3) years, disease duration of 14.8 (9.6) years, and median (interquartile range) EDSS score of 3.5 (2.0–4.4). Moderate to weak correlations were found between daily step count and IPAQ total MET min/week, MVPA MET-min/week, and walking MET-min/week in the total cohort. Time spent sitting was inversely correlated with total MET-min/week and MVPA MET-min/week. Subgroup analysis revealed that daily step count was significantly correlated with total MET-min/week, MVPA MET-min/week, and walking MET-min/week in the “mild disability” subgroup only, whereas time spent sitting was inversely correlated with total MET-min/week ($p < 0.05$, $r = -0.582$) in the “moderate to severe disability” subgroup. There was no association between objectively assessed PA and GLTEQ scores in any group. In the total cohort, moderate to weak correlations were found between daily step count and walking assessments, and the 12-item MS Walking Scale. Moderate to weak correlations were also observed between VO_2peak and walking assessments by Timed 25-Foot Walk and 2-Minute Walk Test. Multiple linear regression analysis identified disability and VO_2peak as predictors of PA. The authors concluded that significant associations of objective PA measurements using accelerometry with IPAQ were found only in pwMS with “mild disability.” In pwMS with “moderate to severe disability,” IPAQ did not reflect the objectively assessed amount of PA. In the study cohort, GLTEQ showed no association with objectively assessed PA [23].

Several authors have investigated the environmental conditions related to reduced PA. Doerksen et al. [24] examined the relationship between environmental characteristics and PA in adults with MS. They found that the presence of shops and supermarkets within walking distance, the presence of a public transport stop within walking distance, and the availability of free or inexpensive forms of recreation were correlated with pedometer readings measuring PA. This indicates the great importance of easy access to recreation [24].

Ploughman [25] reviewed 12 quantitative (total N = 2,627) and nine qualitative (total n = 97) studies concerning the barriers to PA. The barriers were categorized into five domains from greatest to least frequently predictive: (1) MS-related impairment and disability, (2) attitude and outlook, (3) fatigue, (4) knowledge/perceived benefits of exercise, and (5) logistical factors: finances, support, and accessibility. Several approaches to breaking down barriers, such as behavioural modification, peer support, use of technology, and adapted community exercise, showed promise in improving PA participation. The author concluded that physical therapists, other health team members, and volunteers are more likely to be successful in overcoming barriers to PA in MS by working together. Barriers can be addressed concurrently by employing tailored and combined approaches using education, motivational interviewing, exercise practice, and problem-solving [25].

Riemann-Lorenz et al. [26] explored expert views on facilitators and barriers to long-term PA in people with MS. They conducted semi-structured telephone or face-to-face interviews with 12 MS and PA experts (scientists, practitioners, patient representatives) from five European countries. The authors identified 20 themes and categorized them into environmental and personal factors. The most frequently mentioned and intensively discussed themes were environmental factors. The themes were structured according to possible intervention levels: organizational, interpersonal, and intrapersonal. Organizational-level themes included availability, access, and quality of exercise/PA options; health system characteristics such as services and organization, health professionals, and information provision. Interpersonal-level themes included social support and peer support. Disease-related factors were the most frequently mentioned intrapersonal-level theme. In this study, more codes were obtained for environmental factors than for personal factors. The results suggested that environmental factors may need to be addressed in particular to increase long-term PA adherence. Long-term PA among people with MS is subject to a number of modifiable determinants: personal and environmental factors [26].

Dunn et al. [7] reviewed in 1998 the history of lifestyle PA interventions and defined lifestyle PA based on this review. They located 14 studies that met this definition. The authors identified three major issues concerning lifestyle PA interventions: (1) testing their ability to be implemented on a large scale; (2) examining cost-effectiveness for different modes of delivery; and (3) researching efficacy in populations such as the elderly, minorities, economically disadvantaged, and individuals with concurrent disease. More studies aimed at manipulating the environment to increase PA need to be tested over periods of one year or longer. It is possible that lifestyle interventions could be integrated and delivered by new technologies such as interactive computer-mediated programs, telephone, or computer web-based formats. All these recommended approaches should utilize valid and reliable measures of PA and should examine the health effects, particularly on a longitudinal basis. Basic dose-response studies in controlled settings are also needed to help us understand the health effects of accumulated moderate-intensity activity [7].

Stuifbergen [27] studied the relationship of PA to social, mental, and physical health and well-being in persons with MS. A convenience sample of 37 persons with MS completed the Human Activity Profile and the Medical Outcomes Study Short-Form Health Survey. Activity levels in persons with MS were much lower than the norms reported for other groups of healthy adults and adults with a variety of chronic conditions. Higher activity scores were associated with higher scores on the measures of physical functioning and general health. The subgroup of persons who reported engaging in regular exercise had significantly higher scores on the measure of physical functioning than those who did not exercise [27].

Few authors have considered ways to increase PA in patients. Dlugonski et al. [28] observed 21 MS participants who wore an ActiGraph 7164 accelerometer for 7 days and completed the IPAQ and GLTEQ before the study and after a 12-week Internet-based intervention. This behavioural intervention slightly increased PA in accelerometer recordings ($d = 0.68$) and the number of steps ($d = 0.60$). This was associated with a slight increase in PA [28].

Sangelaji et al. [29] performed a systematic review and meta-analysis to evaluate the effectiveness of behaviour change interventions to increase PA participation in people with MS. A total of 19 out of 573 studies were included. The meta-analysis showed that behaviour change interventions can significantly increase PA participation, with a main duration of 8 to 12 weeks. Behaviour change interventions did not significantly impact the physical components of quality of life or fatigue. The authors stated that further high-quality investigations of the efficacy of behaviour change interventions to increase PA in MS are needed [29].

Discussion

For many years, patients with MS, an inflammatory demyelinating disease of the central nervous system, have been advised to avoid physical effort. Described in 1890, Uhthoff's phenomenon (also known as Uhthoff sign or Uhthoff syndrome) is characterized as a temporary, short-lived (less than 24 h), and stereotyped worsening of neurological function among MS patients in response to increases in core body temperature. For over a hundred years, it limited the use of heat and physical exercise in the physiotherapy of these patients – Uhthoff blamed physical exercise for the increase in body temperature of patients. The mechanism of Uhthoff phenomenon is still awaiting explanation [30].

Motl et al. [31] studied the relationship between changes in the individual level of PA, self-efficacy, and health-related quality of life (HRQoL) over a period of one year of observation. The sample consisted of 269 individuals with RRMS. The subjects completed the GLTEQ, the Multiple Sclerosis Self-Efficacy Scale (MSSE) questionnaire, and the Multiple Sclerosis Quality of Life-29 questionnaire twice – before the start of the observation and after a year. Preliminary analysis showed that a change in the individual level of PA was associated with a change in the individual level of quality of life, both in the physical and mental spheres. Subsequent analysis showed that the change in the individual level of self-efficacy in people with MS was associated with a change in the individual level of HRQoL in the physical sphere, while the change in the individual level of self-assessment in the control group was associated with a change in HRQoL in the mental sphere. The individual level of self-assessment of one's fitness was the strongest predictor of changes in quality of life. The authors concluded that PA and self-efficacy may be important targets for subsequent behavioural interventions to improve the quality of life of people with MS, although self-efficacy appears to be more important than PA [31].

Recently, Beratto et al. [32] described the results of a systematic review and meta-analysis on the effect of exercise on mental health and HRQoL in adult persons with MS (PwMS). Forty-nine studies (*n* = 2,057 participants) were included. Exercise improved overall well-being, subjective well-being, social well-being, and HRQoL. The authors concluded that exercise interventions can improve well-being and HRQoL in PwMS. Future studies should focus on PwMS aged ≥ 65 years or with a higher level of impairments [32].

Lately, Jeng et al. [33] presented an updated systematic review and quantitative synthesis of PA levels in MS. A total of 24 studies met the inclusion criteria and yielded a total of 119 comparisons. There was a moderate difference in PA levels between persons with MS and controls, but no significant difference between persons with MS and other clinical populations. Moderating variables included sex, disability status, measurement method, outcome, intensity, and application of an MS-specific cut-point. The authors concluded that PA levels remain significantly lower in persons with MS compared with controls, but the magnitude of difference has become smaller over the past decade. There is a need for continued development of effective PA programs that can reach the broader community with MS [33].

The National MS Society convened clinical and research experts in the fields of MS, exercise, rehabilitation, and PA to reach a consensus on optimal exercise and lifestyle PA recommendations for individuals with MS at disability levels 0–9.0 on the EDSS, and to identify and address barriers and facilitators for participation. Based on current evidence and expert opinion, the Society makes the following recommendations:

– Healthcare providers should endorse and promote the benefits and safety of exercise and lifestyle PA for every person with MS.

– Early evaluation by a physical or occupational therapist or exercise or sport scientist, experienced in MS (hereafter, referred to as "specialists"), is recommended to establish an individualized exercise and/or lifestyle PA plan.

– Taking into account comorbidities and symptom fluctuations, healthcare providers should encourage ≥ 150 min/week of exercise and/or ≥ 150 min/week of lifestyle PA. Progress toward these targets should be gradual, based on the person's abilities, preferences, and safety.

– If disability increases and exercise/PA becomes more challenging, referrals to specialists are essential to ensure safe and appropriate prescriptions. – When physical mobility is very limited, exercise should be facilitated by a trained assistant. – Lifestyle PA is the daily accumulation of at least 30 min of activities, including all planned or unplanned leisure, occupational, or household activities that are at least moderate to vigorous in intensity.

– Exercise is a form of LPA that is usually performed repeatedly over an extended period of time (exercise training) with a specific external objective (e.g., improvement of fitness, physical performance, or health). These activities are distinct from rehabilitation, which is defined as intermittent or ongoing use of interdisciplinary strategies to regain or maintain optimal physical function, promote functional independence, prevent complications, and improve overall quality of life [5].

It is worth emphasizing that in recent years, the WHO has paid growing attention to the association between PA and health, resulting in the creation of a Global Action Plan on Physical Activity 2018–2030 to promote active lifestyles [34]. Also, several scientific articles in the same vein have been published, including the *British Journal of Sports Medicine* special issue on PA. In 2020, Bull et al. [35] presented recommendations on behalf of the WHO experts, advising all adults to engage in 150–300 min of moderate-intensity exercise or 75–150 min of vigorous-intensity exercise per week, or an equivalent combination thereof. The recommendations also stressed that regular muscle-strengthening exercise and reducing sedentary behaviour offer health benefits to people of all ages regardless of circumstances but did not explain precisely how sedentary behaviour should be understood [35].

Summary

Taking into account what was written above, it can be stated that there is evidence that lifestyle PA is important for the successful primary and secondary prevention of MS if practised with moderate and high intensity. According to WHO recommendations, PA should take 150–300 min per week, divided mostly over 3 or 4 days, preferably every day. This activity should be tailored individually by a qualified personal coach. When planning PA, one should take into consideration all contraindications and necessary precautions. The type of PA will depend on the patient's preferences and possibilities, including fitness, as well as economic and local facilities. According to many authors, personalized

PA should be the first-line approach for the secondary prevention of MS.

Potential future developments in the field include the need for investigations according to sophisticated protocols to enrich our knowledge on this subject. Future studies should aim to identify specific types of PA that are particularly recommended for patients with MS.

Ethical approval

The conducted research is not related to either human or animal use.

Disclosure statement

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Conflict of interest

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