

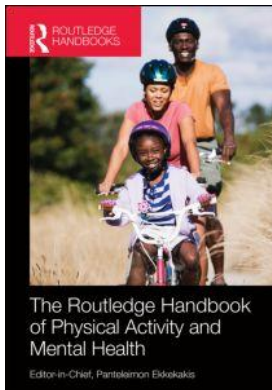
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PHYSICAL ACTIVITY AND QUALITY OF LIFE IN MULTIPLE SCLEROSIS

Robert W. Motl

Multiple sclerosis (MS) is a prevalent, non-traumatic, and chronic disabling neurological disease among adults in the United States and worldwide. The National Multiple Sclerosis Society (NMSS) estimates that there are approximately 400,000 cases of MS in the United States with an incidence of nearly 200 new cases each week (NMSS, 2005). Others have indicated that MS affects an estimated 1 per 1,000 persons in the United States (Mayr et al., 2003). There are an estimated 2.5 million cases of MS worldwide (NMSS, 2005). The majority of people with MS are diagnosed between 20 and 50 years of age, and women are affected between two and three times more often than men (NMSS, 2005). MS is more common among people with northern European ancestry than people of African, Asian, and Hispanic descent (NMSS, 2005).

MS itself is typically characterized by intermittent and unpredictable, but recurrent, episodes of focal inflammation in the central nervous system (CNS; Hemmer, Nessler, Zhou, Kieseier, & Hartung, 2006) that eventually result in the demyelination and transection of axons in the brain, optic nerve, and spinal cord (Trapp & Nave, 2008). The axonal damage interferes with the smooth and rapid propagation of electrical potentials along neuronal pathways in the CNS (Bjartmar & Trapp, 2001). Over the course of the disease, there are further neurodegenerative processes that presumably are characterized by insufficient neurotrophic support rather than inflammation within the CNS, although this latter process is not completely understood (Bjartmar & Trapp, 2001; Trapp & Nave, 2008). The inflammatory and neurodegenerative processes are associated with the accumulation of symptoms, neurological impairment, and disability over time in persons with MS. Symptoms of MS commonly include walking and cognitive impairments, visual and bowel/bladder disturbances, and depression, fatigue, and pain (NMSS, 2005; Riazi et al., 2003). Ultimately, the disease process and its manifestations compromise quality of life (QOL) in persons with MS.

Multiple sclerosis and quality of life

There has been an increased interest by researchers and clinicians in the study of QOL among persons with MS (Benito-León, Morales, Rivera-Navarro, & Mitchell, 2003; Mitchell, Benito-León, Gonzalez, & Rivera-Navarro, 2005). QOL can be described as an umbrella term that consists of a number of outcomes that are considered important within a person's life (Rejeski & Mihalko, 2001). These outcomes can include physical, social, psychological, and spiritual

dimensions of one's well-being (Benito-León et al., 2003). Overall, QOL represents a judgment from the respondent's perspective that reflects how well they are living based on consideration of those dimensions of well-being.

There is a wealth of evidence indicating that persons with MS have lower QOL than other populations, including persons with or without a chronic disease condition (Benito-León et al., 2003; Mitchell et al., 2005). For example, persons with MS had significantly lower overall and domain-specific QOL than controls without a chronic disease in one cross-sectional study (Lobentanz et al., 2004). Other descriptive studies have reported that QOL in persons with MS is reduced even when compared with those who have inflammatory bowel disease, ischemic stroke, and rheumatoid arthritis (Lankhorst et al., 1996; Naess, Beiske, & Myhr, 2008; Rudick, Miller, Clough, Gragg, & Farmer, 1992). Several features of MS likely contribute to compromised QOL, including (1) onset of MS during the most productive years of one's life, (2) uncertain and unstable course of MS, (3) diffuse effects of MS on the CNS and mental processes, and (4) absence of convincing disease-modifying treatment (Benito-León et al., 2003). Obviously, mitigating reductions or even improving QOL is an important objective of clinical research and care of persons with MS. Such goals might be accomplished by understanding the factors that influence QOL in those with MS.

Factors influencing quality of life in multiple sclerosis

There are many modifiable factors that are associated with QOL in persons with MS and such factors represent possible targets or approaches for improving QOL in this population. Disability is one of the primary factors associated with reduced QOL in persons with MS (Amato et al., 2001; Lobentanz et al., 2004; Merkelbach, Sittinger, & Koenig, 2002) and in the context of MS is typically characterized by a restriction or inability to perform ambulatory activities in the manner considered normal. By extension, disability is often measured among persons who have MS by using the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). In previous cross-sectional studies, EDSS scores were negatively correlated with overall QOL and physical aspects of health-related QOL in persons with MS (Amato et al., 2001; Lobentanz et al., 2004). Importantly, the effect of disability on QOL remained statistically significant even when controlling for other factors such as fatigue, cognitive impairment, anxiety, depression, and social support (Henriksson, Fredrikson, Masterman, & Jonsson, 2001; Stuifbergen, Seraphine, & Roberts, 2000).

Based on a prominent literature review, there are other factors such as the mood states of anxiety and depression, self-efficacy, social support, pain, and fatigue that are associated with QOL in those with MS (Mitchell et al., 2005). Mood states, namely anxiety and depression, as measured by the Hospital Anxiety and Depression Scale, have been significantly and negatively correlated with physical and mental aspects of health-related QOL in a cross-sectional study of patients with MS, even after controlling for EDSS scores (Janssens et al., 2003). Another study reported that personal beliefs regarding confidence in coping with challenging situations (i.e., self-efficacy), as measured by the MS Self-Efficacy Scale, were positively associated with physical and psychological aspects of QOL in a cross-sectional study of MS patients (Riazi, Thompson, & Hobart, 2004). Both social support (i.e., a person's perception of support and assistance from family, friends, and acquaintances) and self-efficacy were positively associated with overall QOL in a cross-sectional sample of 786 persons with MS, even after controlling for disability (Stuifbergen et al., 2000). Pain, as assessed by the McGill Pain Questionnaire, was inversely correlated with aspects of QOL in two recent cross-sectional studies of persons with MS (Kalia & O'Connor, 2005; Svendsen, Jensen, Hansen, & Bach, 2005). Fatigue assessed by the Fatigue

Severity Scale has been negatively correlated with aspects of QOL in cross-sectional studies of MS patients (Benedict et al., 2005; Lobentanz et al., 2004). Collectively, these findings are consistent with the notion that anxiety, depression, self-efficacy, social support, pain, and fatigue are additional modifiable factors that are associated with QOL in persons with MS (Benito-León et al., 2003; Stuifbergen & Roberts, 1997).

There is a wealth of evidence on factors associated with QOL in persons with MS, but until recently researchers had not examined the possible association between co-occurring or symptom clusters and QOL in this population. Symptom clusters have been defined as “three or more concurrent symptoms (e.g., pain, fatigue, sleep insufficiency) that are related to each other” (Dodd, Miaskowski, & Paul, 2001, p. 465). Symptom clusters consist of multiple symptoms that are interrelated through a common etiology or statistically as a cluster or latent variable (Miaskowski, Dodd, & Lee, 2004). Conceptually, the study of symptom clusters recognizes that co-occurring symptoms likely provide a better understanding of consequences (e.g., behavior, function, or QOL) compared with a single symptom. To that end, one study examined the symptom cluster of fatigue, pain, and depression as a correlate of reduced QOL in persons with MS (Motl & McAuley, 2010). The sample included 291 persons with a definite diagnosis of MS who were enrolled in a 6-month longitudinal study of physical activity and QOL. The participants completed baseline measures of fatigue, depression, and pain and follow-up measures of QOL. Cluster analysis initially identified three subgroups differing in experiences of fatigue, depression, and pain. Analysis of variance then indicated that the subgroup with the lowest scores on all three symptoms had the highest QOL, whereas the subgroup with the highest scores on the symptoms had the worst QOL. Such findings provide preliminary support for fatigue, pain, and depression as a symptom cluster that predicts reduced QOL in persons with MS.

Another study subsequently replicated those findings with a slightly broader symptom cluster of fatigue, pain, depression, and perceived cognitive complaints, and examined its association with QOL in 133 persons with a definite diagnosis of MS (Motl, Suh, & Weikert, 2010). Results indicated that (1) there were moderate bivariate correlations between fatigue, depression, pain, and perceived cognitive complaint scores; (2) the correlations between scores from the pairs of symptoms were attenuated when expressed as partial correlations controlling for the covariance of the remaining pair of symptoms; (3) exploratory and confirmatory factor analyses supported a single-factor model for the associations among fatigue, depression, pain, and perceived cognitive complaint scores; (4) cluster analysis identified three subgroups differing in experiences of fatigue, depression, pain, and perceived cognitive complaints; and (5) analysis of variance indicated a possible dose-response relationship between worsening symptoms and decreases in the psychological and physical domains of QOL. Such findings provide initial support for a possible dose-response relationship between worsening symptoms of fatigue, pain, depression, and perceived cognitive complaints with QOL in persons with MS.

Lifestyle factors such as physical activity, spiritual growth, health responsibility, interpersonal relations, nutrition, and stress management have been associated with QOL in persons with MS (Stuifbergen, 1995; Stuifbergen et al., 2000). For example, participation in lifestyle activities to improve overall health and well-being, as measured by overall scores on the Health Promotion Lifestyle Profile II, was positively and weakly to moderately associated with increased QOL in small (Stuifbergen, 1995) and large (Stuifbergen et al., 2000) samples of persons with MS, even after controlling for disability, perceived barriers, self-efficacy, and social support. One particular lifestyle factor that has been identified as important for QOL in MS is physical activity.

Physical activity and quality of life

Physical activity is a lifestyle factor that has been associated with many benefits among persons living with MS. The benefits of physical activity for persons with MS have been summarized in a general literature review (Garrett & Coote, 2009), a systematic Cochrane review (Rietberg, Brooks, Uitdehaag, & Kwakkel, 2005), and meta-analyses (Motl & Gosney, 2008; Snook & Motl, 2009). Some of the benefits of physical activity in persons with MS include improved strength, body composition, and cardiorespiratory fitness as well as management of fatigue, depression, anxiety, and cognitive impairment. One meta-analysis indicated that physical activity, in the form of exercise training, was associated with improved walking mobility in persons with MS (Snook & Motl, 2009). This body of literature is important as it identifies that physical activity is associated with important disease-specific benefits among those with MS.

Physical activity may have additional benefits relative to QOL. This is noteworthy as MS is associated with a reduction in QOL (Benito-León et al., 2003) and an improvement in QOL through an active lifestyle might be an even more meaningful outcome than general health benefits for those with MS (Benito-León, 2011). Descriptive, cross-sectional, and experimental evidence links physical activity, exercise training, and QOL among persons with MS. Stuijbergen (1997) conducted a descriptive study that focused on physical activity and QOL in those with MS. This descriptive study ($N = 37$) reported a positive relationship between physical activity and QOL as measured by the general health and physical functioning components of the SF-36 and weaker correlations with the vitality and social functioning components of the same scale. The effect of physical activity on QOL in this study was not limited to structured exercise programs, but generalized to forms of physical activity such as gardening and housework. However, these findings should be interpreted with caution given the small sample size, descriptive research design, and use of a self-report physical activity measure. Self-report physical activity measures have been criticized for issues of poor reliability and validity, whereas objective measures presumably have fewer psychometric issues (Dishman, Washburn, & Schoeller, 2001).

Recent cross-sectional studies have provided additional evidence of an association between physical activity and QOL in MS. One study examined the association between self-reported and objectively measured physical activity and QOL, using generic and disease-targeted instruments, in persons with MS (Motl, McAuley, Snook, & Gliottoni, 2008). The results from this cross-sectional analysis indicated that physical activity was positively associated with QOL, and this did not differ based on type of physical activity measure or QOL instrument. Another cross-sectional study reported that physical activity was favorably associated with QOL in a sample of 121 patients with MS (Stroud & Minahan, 2009). Such findings are stronger than descriptive studies, but should be interpreted with caution given the cross-sectional nature of the research designs and lack of evidence on the temporal nature of the association among variables.

Multiple intervention studies have examined the effect of exercise training programs on various indices of QOL in MS. Petajan et al. (1996) examined the effects of a 15-week aerobic training intervention versus a non-exercise control condition on mood, daily activities, and fatigue among 54 persons with MS. The exercise intervention was associated with transient improvements in depression and anger mood scores, prolonged improvements in daily activity scores on variables such as social interaction, emotional behavior, and home management, and no effect on fatigue severity scores. This study provided evidence that exercise training influenced factors related to QOL, although the study did not actually measure QOL and did not account for social interaction among participants (Sutherland, Andersen, & Stooove, 2001).

Sutherland et al. (2001) demonstrated that a 10-week aerobic exercise intervention resulted in improvements in physical, social, and mental components of QOL as measured by the Multiple

Sclerosis Quality of Life-54 scale. Mostert and Kesselring (2002) reported that a 4-week aerobic training intervention resulted in improvements on only two dimensions of the SF-36, vitality and social function, among MS patients. Similar improvements in vitality were reported after a 6-month program of yoga and aerobic exercise among individuals with MS (Oken et al., 2004). One final study reported positive effects of an 8-week aerobic training intervention on QOL as measured by the Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) (Schulz et al., 2004). There were relatively modest, though statistically significant, improvements in social function, mood, and total scores on the HAQUAMS in the exercise-training group. We note, however, that these intervention studies generally focused on aerobic exercise programs instead of lifestyle physical activity and included small samples of persons with MS. The intervention studies generally focused on QOL as a subsidiary, rather than primary, study outcome.

Using meta-analytic procedures, one study examined the overall effect of exercise training interventions on QOL among persons with MS (Motl & Gosney, 2008). To do this, the researchers searched MEDLINE, PsychINFO, and Current Contents Plus for the period of 1960 to November 2006 using the keywords exercise, physical activity, and physical fitness in conjunction with QOL and MS. The researchers further conducted a manual search of bibliographies of retrieved papers and literature reviews, and contacted study authors about additional studies. Twenty-five journal articles were located and reviewed, of which only 13 provided enough data to compute effect sizes expressed as Cohen's *d*. The 13 studies with 484 MS participants yielded 109 effect sizes with a weighted mean effect size of $g = 0.23$ (95% CI = 0.15, 0.31). There were larger effects associated with MS-specific measures of QOL when compared with general measures of QOL. The nature of the exercise stimulus further influenced the magnitude of the mean effect size, with aerobic exercise yielding the largest effects on QOL. The cumulative evidence from the meta-analysis supports that exercise training is associated with a small improvement in QOL among persons with MS; there currently is not evidence from interventions on lifestyle physical activity and improvements in QOL among those with MS.

Factors accounting for the positive association between physical activity and QOL

Previously identified factors such as disability, mood, self-efficacy, social support, and pain might account for the association between physical activity and QOL in persons with MS. This proposition was initially based on conceptual arguments and supported by empirical research involving older adults. For example, disability might account for the relationship between physical activity and QOL among those with MS. This possibility is best conceptualized within Nagi's (1965) disablement model. The disablement model and its operational definitions (Verbrugge & Jette, 1994) describe the pathway from disease to disability. The pathway involves the transition from (1) pathology (i.e., disease) to impairment (i.e., dysfunction in specific body systems), (2) impairment to functional limitation (i.e., restrictions in basic physical and mental actions), and (3) functional limitation to disability (i.e., difficulty with activities of daily life). Physical activity influences this process through effects on transitions from impairment to functional limitation and functional limitation to disability (Guralnik & Ferrucci, 2003; Stewart, 2003). The stunting of the disability process might enhance QOL and provide a basis for examining the indirect effect of physical activity on QOL through disability. Physical activity, disability, and QOL have been related among those with MS (NMSS, 2005; Pearson, Busse, van Deursen, & Wiles, 2003, 2004; Stuijbergen, 1997), and support an examination of the indirect effect of physical activity on QOL through disability in this population.

Psychological factors such as self-efficacy and self-esteem might account for the effect of physical activity on QOL in those with MS. Such a position has been proposed by Stewart and King (1991) and supported empirically in research by Elavsky et al. (2005) and McAuley et al. (2006). Indeed, Stewart and King (1991) conceptualized a comprehensive framework of QOL outcomes of relevance for physical activity research with older adults. This framework views function and well-being as two broad QOL categories with several underlying elements (e.g., physical, cognitive, emotional). This conceptualization has its basis in the Medical Outcomes Study and its seminal measure the Short-Form 36 or SF-36. As noted by Rejeski and Mihalko (2001), QOL in such a framework represents an umbrella term for multiple positive outcomes. These multiple positive outcomes allow for an inference or judgment of QOL. The underlying elements of such a model are specific, proximal outcomes of physical activity and may be viewed as intermediate factors in a broader model that includes global, distal QOL constructs. Such proximal effects of physical activity influence more distal QOL constructs (Rejeski & Mihalko, 2001).

This proposition was recently examined in two studies of mediators of the association between physical activity and QOL among older adults (Elavsky et al., 2005; McAuley et al., 2006). Participants in one study completed psychosocial and QOL measures at 1 and 5 years following enrollment in a 6-month randomized controlled exercise trial. The analyses indicated that (1) physical activity was cross-sectionally associated with self-efficacy, self-esteem, and positive affect, and, in turn, self-efficacy and positive affect were associated with QOL, and (2) changes in physical activity were associated with changes in self-esteem and positive affect, but only change in positive affect was associated with change in QOL. The other study examined the associations among physical activity, health status, self-efficacy, and QOL in older Black and White women as part of the baseline assessment of a 24-month prospective study (McAuley et al., 2006). The analyses indicated that physical activity was indirectly associated with QOL through a pathway that included self-efficacy and health status. Such findings support the position that physical activity effects on QOL are indirect and provided seminal support for a social-cognitive perspective on the association between physical activity and QOL in older adults.

Based on conceptual arguments and the empirical research with older adults, one study examined variables that might account for the relationship between physical activity and QOL in a sample ($N = 292$) of persons with a definite diagnosis of MS (Motl, McAuley, Snook, & Gliottoni, 2009). The participants wore an accelerometer for 7 days and then completed self-report measures of physical activity, QOL, disability, fatigue, mood, pain, self-efficacy, and social support. Covariance modeling indicated that those who were more physically active reported lower levels of disability ($\gamma = -.50$), depression ($\gamma = -.31$), fatigue ($\gamma = -.46$), and pain ($\gamma = -.19$), and higher levels of social support ($\gamma = .20$), self-efficacy for managing MS ($\gamma = .41$), and self-efficacy for regular physical activity ($\gamma = .49$). Those who reported lower levels of depression ($\beta = -.37$), anxiety ($\beta = -.15$), fatigue ($\beta = -.16$), and pain ($\beta = -.08$) and higher levels of social support ($\beta = .26$) and self-efficacy for controlling MS ($\beta = .17$) reported higher levels of QOL. The observed pattern of relationships supports the possibility that physical activity is indirectly associated with improved QOL in persons with MS via depression, fatigue, pain, social support, and self-efficacy for managing MS.

Those findings were then replicated in a prospective examination of depression, fatigue, pain, self-efficacy, and social support as possible intermediaries in the pathway between changes in physical activity and QOL over a 6-month period of time in persons with MS (Motl & McAuley, 2009). Adults with a definite diagnosis of MS wore an accelerometer for 7 days and then completed a battery of questionnaires at baseline ($N = 292$) and 6-months' follow-up ($N = 276$). The initial data analysis indicated that change in physical activity was associated with a statistically

significant and small residual change in QOL ($\beta = .07$). The subsequent data analysis indicated that change in physical activity was associated with residual changes in fatigue ($\gamma = -.17$), pain ($\gamma = -.13$), social support ($\gamma = .07$), and self-efficacy ($\gamma = .11$), and, in turn, changes in fatigue ($\beta = -.13$), pain ($\beta = -.09$), social support ($\beta = .18$), and self-efficacy ($\beta = .10$) were associated with a residual change in QOL. The observed pattern of associations supports the possibility that physical activity is indirectly associated with improved QOL through pathways that include fatigue, pain, social support, and self-efficacy in persons with MS.

One other study focused specifically on the role of self-efficacy in the association between physical activity and QOL in MS (Motl & Snook, 2008). This was based on evidence that self-efficacy and physical activity have been positively associated with QOL in persons with MS, and using a social-cognitive perspective (McAuley et al., 2006), the association between physical activity and QOL might be indirect and accounted for by self-efficacy. The study tested the hypothesis that physical activity would be indirectly associated with QOL through a pathway that included self-efficacy. Participants were 133 persons with a definite diagnosis of MS who completed the Godin Leisure-Time Exercise Questionnaire, Multiple Sclerosis Self-Efficacy Scale, and Multiple Sclerosis Impact Scale. Path analysis indicated that those with MS who were more physically active had greater self-efficacy for function and control, and self-efficacy for function and control were associated with greater physical and psychological components of QOL. Such findings further support physical activity as a possible modifiable behavior for mitigating reductions of QOL by improving self-efficacy in persons with MS.

Limitations of existing research

There is an emerging body of research on physical activity and QOL in MS, but not all researchers have considered the evidence compelling based on methodological challenges (Mayo & Asano, 2009). Indeed, this area of exercise in MS has been plagued by challenges including choosing and prioritizing the outcomes, designing and dosing the intervention to target the focal outcome, monitoring and ensuring compliance with the intervention, and recruiting an appropriate sample based on a power analysis (Mayo & Asano, 2009). This is countered by other recommendations that promotion of physical activity represents a critical part of the clinical armamentarium of clinicians who manage the consequences of MS (Benito-León, 2011). Collectively, there is not yet universal agreement, but continued investigation, perhaps within the context of a large multi-centered randomized controlled trial, will highlight the value of exercise and physical activity in the lives of persons with MS.

Next steps

Previous studies have provided evidence for the range of factors influencing QOL in persons with MS. Physical activity is one modifiable behavior that has been consistently associated with QOL in descriptive, cross-sectional, and longitudinal studies, and intervention studies have further demonstrated favorable effects of exercise training on QOL in persons with MS. Despite the beneficial effects of exercise training on QOL, this type of physical activity may present many barriers for persons with MS including accessibility, cost, and the need for specialized staff and equipment. The focus on exercise training might explain the high rate of sedentary behavior among persons with MS (Motl, McAuley, & Snook, 2005). By comparison, lifestyle physical activity that occurs in the context of the daily lives of persons with MS might represent a more accessible and reasonable interventional target for improving QOL and achieving other benefits in persons with MS. To date, there is a lack of intervention studies that targeted an increase in

lifestyle physical activity as an approach for improving QOL or other outcomes among persons with MS. We are aware of two studies that have demonstrated an increase in self-reported (Motl, Dlugonski, Wójcicki, McAuley, & Mohr, 2011) and objective physical activity (Dlugonski, Motl, & McAuley, 2011) after participation in a 12-week Internet-based behavioral intervention among persons with MS. Perhaps future studies should adopt a similar behavioral approach for increasing physical activity and examining its influence on QOL and other meaningful outcomes in persons with MS. QOL is a putative meaningful benefit associated with living an active lifestyle that researchers should continue exploring in order to improve the overall health and well-being of persons with MS.

Summary

MS is associated with a substantial reduction in QOL (Miltenburger & Kobelt, 2002). This is likely caused by (1) onset of MS during the most productive years of life, (2) uncertain and unstable course of MS, (3) diffuse effects of MS on the CNS and mental processes, and (4) absence of a convincing disease-modifying treatment (Benito-León et al., 2003). QOL has been identified as a key outcome variable in clinical research and practice of those living with MS. Physical activity is a modifiable lifestyle factor that is favorably associated with QOL in those with MS. The significance of this observation is that physical activity has a potentially strong role to play in improving the QOL of those with MS. Encouraging physical activity among those with MS, although challenging, is potentially crucial for improvements in QOL. There is further benefit in that physical activity is an inexpensive option for limiting disability and improving QOL with potential economic and personal payoffs for those with MS. This is significant as there is a link between the costs of MS and QOL (Henriksson et al., 2001; McCabe & De Judicibus, 2005; Miltenburger & Kobelt, 2002).

By further examining the physical activity and QOL relationship, we might be in a better position for designing activity programs that maximize QOL benefits. In particular, future research should seek to better understand the effects of lifestyle physical activity, not solely exercise behavior, on QOL in persons with MS. Physical activity is a modifiable lifestyle factor, and provides researchers and clinicians with an effective, non-pharmacological approach for increasing QOL in those with MS. Researchers and clinicians might be able to identify and then manipulate environmental, social, or personal variables in an effort to increase physical activity and induce QOL benefits. This translational component obviously requires studies that examine correlates of physical activity in those with MS and, ultimately, the design of interventions to promote factors associated with the improvement of QOL in persons with MS. Researchers have made great strides in identifying correlates and designing behavioral interventions, and continued research will highlight the efficacy of such approaches for increasing physical activity and improving the QOL of persons living with MS.

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