Exercise, Physical Activity, and Sedentary Behavior in the Treatment of Depression: Broadening the Scientific Perspectives and Clinical Opportunities

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Research exploring links between exercise and depression now span several decades, yet several clinically relevant research questions remain unanswered. This opinion article briefly describes the status of selected research issues from the exercise depression literature and offer insights into research areas that are currently lacking. We draw particular attention to the potential of research exploring links between sedentary behavior and depression.

BENEFITS OF EXERCISE INTERVENTIONS IN DEPRESSION: EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS

To date, the strongest evidence on the benefits of physical activity in depression comes from randomized controlled trials (RCTs), in which changes in depression severity have been assessed before and after a prescribed exercise intervention (1). Meta-analytic reviews have supported the antidepressant effects of exercise among otherwise healthy adults (2), chronically ill patients (3), and patients with depressive disorders (4). Three recent Cochrane reviews have each concluded that exercise is moderately more effective than a control intervention for reducing depression symptoms (standardized mean difference from 35 trials = −0.62) (4–6). For example, in a multicentre trial involving 2322 patients treated for heart failure, Blumenthal et al. (7) randomized participants to either 12 months of supervised home-based aerobic exercise or usual depression treatment (no planned exercise). Compared with usual care, aerobic exercise resulted in a modest but statistically significant reduction in mean depression scores at both 3- and 12-month follow-up (7). In an often cited efficacy study, Dunn et al. explored dose–response relationships to exercise in 80 adults aged 20–45 years with mild-to-moderate depression (1). Participants were randomized to one of the four supervised exercise treatment groups lasting 12 weeks or a control condition. The findings demonstrated that exercise by itself, in amounts equivalent to consensus public health recommendations, is effective in the treatment of depression.

Recently, physical exercise interventions have also been compared to Internet-delivered treatments for depression. In the largest community-based effectiveness trial of exercise for depression, Hallgren et al. randomized 946 outpatients to one of the three 12-week interventions: prescribed physical

exercise, Internet-based cognitive behavioral therapy (ICBT), and usual care by a physician, consisting of brief CBT-focused therapy and antidepressant treatment (8). Supervised aerobic exercise and stretching classes were offered to participants three times per week for 12 weeks. At posttreatment, patients randomized to the exercise intervention reported significantly lower depression severity, compared to usual care, and the improvements were equivalent to those seen in the ICBT group (8).

NON-EXERCISE PHYSICAL ACTIVITY AND DEPRESSION: BROADENING THE PERSPECTIVE

This experimental research provides clinically relevant information about the effects of prescribed *exercise* on mental health outcomes. However, exercise is only one subtype of physical activity, involving planned, repetitive movement, purposefully engaged in to improve fitness and/or health (9). Physical activity has a broader definition and includes all forms of daily movement that result in energy expenditure above resting levels (9). Thus, total physical activity comprises the sum of non-exercise activities (e.g., housework and gardening) and exercise activities (e.g., running and weight training). Importantly, these non-exercise activities contribute a much larger proportion to overall energy expenditure than planned exercise does on a daily basis (10).

Cross-sectional studies have shown that depressed adults are significantly less active than non-depressed adults (11, 12). On average, physically active people have nearly 45% lower odds of experiencing depression symptoms compared to inactive people (13). Several large prospective cohort studies have reported inverse associations between physical activity and depressive symptoms (14, 15), highlighting the important relationship between habitual physical activity levels (as distinct from structured exercise programs) and depression severity in adults. For example, Gudmundsson et al. (16) prospectively followed 676 women over 32 years (1974–2005) with self-report measures of physical activity and depressive symptoms. At baseline, lower levels of activity were associated with higher depression scores and those with decreasing activity levels over a time reported significantly higher depression severity scores at follow-up (16). In another study, Lindwall et al. examined prospective associations between physical activity levels and mental health in 3717 healthcare workers (mean age = 46.9 years) across four measurement points spanning 6 years; positive changes in physical activity were associated with positive changes in depression, anxiety, and burnout across time (17).

A notable limitation of previous longitudinal research is that the majority of studies have explored associations of physical activity with depression in non-clinical samples. Indeed, a recent systematic review of 30 prospective studies by Mammen and Faulkner reported that baseline physical activity was negatively associated with the risk of subsequent depression in 25 out of 30 non-clinical, community-based studies (18). This review provides useful information about the relationship between physical activity and the *onset* of depressive illness in otherwise healthy individuals.

However, an equally important question is whether habitual physical activity levels predict the response to depression treatment in individuals who are undergoing treatment. Harris et al. found that higher levels of leisure-time physical activity in 424 depressed adults were associated with lower levels of depression at four assessment points spanning 10 years (19). As in previous studies, however, the authors focused on longitudinal associations generally, rather than the relationship between baseline physical activity levels and the response to depression treatment *per se*.

SEDENTARY BEHAVIOR AND DEPRESSION: TOO LITTLE EXERCISE *AND* TOO MUCH SITTING

Related to physical activity, sedentary behavior refers to any waking activity characterized by an energy expenditure of ≤1.5 metabolic equivalents and a sitting or reclining posture (20). Common sedentary behaviors include TV viewing, computer use, driving, and reading. High levels of sedentary time have been linked detrimentally with cardiovascular disease, diabetes, and premature mortality (21, 22). Recent studies have also demonstrated associations between sedentary behavior and mental health. In a meta-analysis, Zhai et al. reported that sedentary behavior is significantly associated with an increased risk of depression (23). The pooled risk ratios of depression for sedentary behavior were 1.31 (95% CI = 1.16–1.48) in 13 cross-sectional studies and 1.14 (95% CI = 1.06–1.21) in 11 longitudinal studies.

Liu et al. conducted the first meta-analysis examining associations between "screen time" (a measure of sedentary behavior based on time spent using computers and smartphones) and depression in children and adolescents (24). The analysis examined 12 cross-sectional and 4 longitudinal studies (including 1 cohort study). Results indicated that screen time was associated with depression in a non-linear dose–response manner. The authors concluded that further prospective studies are needed to determine whether mutual causality exists between this key measure of inactivity and depression in young people (24). More generally, Liu et al. (24) review highlighted a need to move down the age spectrum to assess these relationships in adolescents, where it may be particularly important to examine interrelations among the factors known to be important in adult depression.

CHANGING SEDENTARY BEHAVIOR IN DEPRESSION: A RESEARCH PRIORITY

Evidence supporting an association between sedentary behavior and depression in adults is growing but currently limited by methodological weaknesses (21). Moreover, studies linking changes in objectively assessed sedentary behaviors with treatment success in depression are currently lacking. Specifically, no studies have compared the effectiveness of a traditional exercise intervention for depression, with an intervention targeting reductions in sedentary behavior. Given the current uncertainty regarding the optimal "dose" of exercise needed to optimize treatment response, an important research question is whether

increases in moderate-to-vigorous exercise are necessary to reduce depression or whether equivalent improvements can be achieved through programs that encourage individuals to "move more and sit less." Current public health guidelines (25) and the bulk of scientific evidence support the former treatment recommendation (4), yet depression interventions targeting sedentary behavior remain absent.

Such research questions could be addressed through RCTs, with the aim of examining the effectiveness of physical activity interventions targeting sedentary behavior, and through prospective cohort studies, where the same individuals are tracked over time using objective assessments of daily activity. RCTs should be adequately powered, should involve an active control group (treatment as usual), and should include long-term follow-up assessments to determine the maintenance of treatment response.

EXERCISE, PHYSICAL ACTIVITY, SEDENTARY BEHAVIOR, AND DEPRESSION: CLARIFYING UNDERLYING MECHANISMS

The mechanisms underlying relationships of exercise, physical activity, and sedentary behavior with improved depression remain understudied. A myriad of biologically plausible factors have been implicated as putative exercise-related mechanisms, including altered 5-HT, NE, and BDNF (26, 27), increased hippocampal cell proliferation (28, 29), and reduced levels of proinflammatory cytokines (30). The 5-HT system may be particularly important to exercise-induced improvements. Changes in brain 5-HT have been shown following acute and chronic exercise in rats (26). In humans, exercise is thought to alter 5-HT release and metabolism in the brain through increased free fatty acid levels during exercise, which stimulate the potential for enhanced 5-HT synthesis (31). In addition, inflammatory processes may directly and indirectly affect the development and treatment of depression *via* influences on the 5-HT system and interactions with adiposity. Cytokine activation of indoleamine-2,3-dioxygenase leads to relative depletion of tryptophan (TRP) and accumulation of kynurenine (KYN), a neurotoxic by-product shown to induce depression (32). Importantly, recent evidence suggested that skeletal muscle PGC-1α1 induced by exercise training alters KYN metabolism and may protect against stress-induced depression (33). The authors reported that reducing plasma KYN in rats protects the brain from stress-induced changes associated with depression (33).

Higher levels of adiposity may function as both a precursor and a consequence of depression, reflecting a bidirectional relationship that may be driven partly by inflammation (34). For example, the KYN/TRP ratio, which conveys changes in both peripheral blood and brain (35), was found to be significantly higher among overweight/obese adults compared to normal weight controls (36) and has been associated with both depression (37) and obesity (36). Thus, inflammatory markers, particularly in the context of increased adiposity, may contribute to depression, putatively, through interactions with the 5-HT system.

For sedentary behavior, there is evidence – albeit not specifically in the context of depression – identifying relationships with C-reactive protein and other inflammation-related markers (38, 39). However, the independent effects and interaction of inflammatory factors, the 5-HT system, and adiposity have remained unstudied as mechanisms of the antidepressant effects of physical activity and exercise, and clearly warrant future research, particularly as these may be influenced by changing sedentary behaviors.

CONCLUSION

In sum, evidence-based treatment for depression continues to expand, but successful treatment and maintenance of treatment response remain limited. Thus, there is a continued need for research into factors that predict successful treatment outcomes. Further research is certainly needed into the effects of planned exercise on depression, including the optimal dose–response and underlying causal mechanisms. However, additional longitudinal studies are also necessary to better understand the complex relationship between habitual physical activity, sedentary behavior, and depression severity. Importantly, these investigations should include children and adolescents. Studies that attempt to assess how changes in levels of activity and inactivity may moderate/mediate the response to empirically supported depression treatments will be particularly relevant. From a public health perspective, it may also be relevant to determine whether those who meet the minimum physical activity levels recommended for general health (40) respond with lower depression severity posttreatment compared to those who do not meet these recommended levels.

With the emerging evidence on the distinct impacts of health outcomes on sedentary behavior – too much sitting as distinct from too little exercise – there is an even broader focus on the overall physical activity spectrum, including the light-intensity physical activities that can displace significant amounts of sedentary time (41). Such broader perspectives on physical activity in the context of depression could be used by clinicians when formulating treatment plans with the goal of maximizing therapeutic benefits, while minimizing the risk of relapse.

Interventions that encourage an overall lifestyle change oriented toward more activity and less sedentary behavior will likely benefit this patient group. However, further research is needed to better understand the plausibly influential roles of both activity and inactivity in this prevalent disorder.

AUTHOR CONTRIBUTIONS

Mats Hallgren initiated the article and wrote the first draft. All coauthors provided input into subsequent revisions.

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