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# The Role of Physical Activity in the Treatment and Prevention of Depression Mediated by Immune Modulatory Effects

**Harris A Eyre[1,2], Kristy Sanderson[3] and Bernhard T Baune[1]***

[1]*Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, Australia*
[2]*School of Medicine and Dentistry, James Cook University, Townsville, Australia*
[3]*Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia*

## Abstract

Depression is a major public health concern and a global priority for research and development. The role of Physical Activity (PA) in the treatment and prevention of psychiatric disorders (e.g. depression, anxiety disorders, bipolar disorder and age-related cognitive dysfunction) has been developing in recent times with a significant number of quality trials emerging. This paper aims to provide an up-to-date, critical assessment of the epidemiological, clinical trial and a focus of clinical immunological evidence for PA interventions in the treatment and prevention of depression. A review of the literature suggests higher levels of PA and Cardio-Respiratory Fitness (CRF) are associated with lower levels of depressive symptoms, lower incidence of depression and lower levels of inflammation. Clinical trials suggest that aerobic, resistance and mind-body PA types may be therapeutic in the treatment of sub-syndromal and major depression, as well as relapse prevention. Clinical neuroscience studies suggest, among other mechanisms, PA may be anti-inflammatory – with PA subtypes having varying anti-inflammatory effects – and this may be associated with clinical efficacy, as well as personalized treatment approaches. This paper proposes an integrated epidemiological, clinical and neuroscience research approach to this field in order to enhance the efficacy of preventive measures in the future.

**Keywords:** Exercise; Physical activity; Prevention; Translational; Epidemiology; Clinical trial; Neuroscience

## Introduction

Depression is a major public health concern and a global priority for research and development [1,2]. Unipolar depressive disorder is predicted to rise from the third leading cause of global burden of disease in 2004 to number one in 2030 [3]. Depression is a prevalent condition with a 12-month prevalence rate of more than 5% in most high-, middle- and low-income countries [4]. It generates substantial loss of quality of life, morbidity, despair and loss of productivity. Depression has been found to increase the risk of all-cause mortality [5].

Alongside the issue of depression is the global concern regarding physical inactivity and metabolic syndrome [6,7]. Physical inactivity is now the fourth leading cause of death worldwide and is thought to have increased in prevalence worldwide due to reducing rates of incidental, transportation-related and occupational PA [6,8]. Physical inactivity is a major causative factor in a large number of major diseases (i.e. coronary heart disease, type 2 diabetes mellitus, breast and colon cancer) and premature mortality [6]. Interestingly, recent data has emerged to suggest that physical inactivity and depression are closely inter-related [9]. Physical inactivity and lower fitness levels may increase the risk of depression and depression may increase the risk of physical inactivity [10-20].

The role of Physical Activity (PA) in the treatment and prevention of psychiatric disorders (e.g. anxiety disorders, bipolar disorder and age-related cognitive dysfunction) has been developing in recent times with a significant number of quality trials emerging [21-25]. Indeed, PA is seen as an efficacious treatment strategy in depression, as well as a preventive strategy, however other studies show no effect [21,26]. PA is defined as "any bodily movement produced by skeletal muscles that requires energy expenditure" while physical exercise is "a subcategory of PA that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective" [27]. PA subtypes include aerobic, resistance, flexibility, neuromotor (e.g. involving balance, agility and co-ordination), mind-body (e.g. tai chi, qi gong and yoga; combining neuromotor, flexibility and meditation), exer-gaming (entertaining video games that combine game play with exercise) and mixed [28-35].

The clinical utility of PA appears to be manifold. PA may be used as a stand-alone treatment, as well as an adjunct for mild to moderate depression [31,36,37]. PA may also has a role in the treatment and prevention of other significant cardio-metabolic disorders, often co-occurring with depression, (i.e. cardiovascular disease, obesity and diabetes mellitus) [38-42]. In the treatment of late-life depression, PA is shown to prevent falls in the elderly via enhancing strength, flexibility and balance [43]. Strategies to increase PA levels can occur in a variety of settings, from the traditional clinical setting, to broader public health initiatives such as large-scale informational dissemination, environmental re-design and policy approaches [44]. From a mechanistic perspective, PA may exert it's effects via a number of positive effects on neurobiological systems,(i.e. increasing production of serotonin (5-HT), Noradrenaline (NA) and Dopamine (DA), increasing Hippocampal (HC) neuroplasticity, reducing neuroinflammation and reduced microglial activation) [21]. Understanding the variety of strategies to increase PA levels, as well as the underlying neurobiological effects of PA is important to progress this field.

This paper aims to provide an up-to-date, critical assessment of

***Corresponding author:** Bernhard T Baune, Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, SA 5005, Australia, Tel: +61 8 8222 5141; Fax: +61 8 8222 2865; E-mail: Bernhard.Baune@Adelaide.edu.au

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the epidemiological, clinical trial and clinical immunological evidence for PA interventions in the treatment and prevention of depression. A review integrating epidemiological, clinical and neuroscience evidence for PA in the treatment and prevention of depression is novel in the literature.

## Methods

This paper is a narrative review. It has utilized search engines Google Scholar, PubMed and ScienceDirect. Keywords in the searches included various combinations of the following key words (i.e. physical activity, exercise, clinical, public health, neuroscience, population, epidemiology, and depression).

## Clinical Implications of Prevention Science in Depression

Prior to investigating the role of PA in the prevention of depression, it is important to first frame the clinical implications of preventive science-based approaches in depression. It is important to identify the types of preventive approaches, the various populations under investigation and the end point of preventive approaches.

When conceptualizing approaches in prevention science, the most commonly used models are those of the Institute of Medicine and the World Health Organization's (WHO) framework of levels of prevention (i.e. primary, secondary and tertiary prevention) [45,46]. A report from the Institute of Medicine suggests prevention may be directed toward the whole population (universal prevention), high-risk groups (selective prevention), or those with subsyndromal symptoms (indicated prevention) [45]. The WHO's prevention framework suggests primary prevention involves strategies aimed at preventing the development of disease; secondary prevention involves strategies to diagnose and treat existent disease in early stages before significant morbidity occurs; and, tertiary prevention involves strategies to reduce negative impact of existent disease by restoring function and reducing disease-related complications [46]. Table 1 outlines these conceptual frameworks of preventive science, as well as clinical examples for the field of PA in the treatment and prevention of depression.

## Evidence for a Role of Physical Activity in the Treatment and Prevention of Depression

There are a number of levels of evidence to be considered when investigating the role of physical activity in the prevention of depression. This level of evidence can be conceptualized as public health, clinical and basic science evidence. In Table 2 we outline these levels of evidence. In Table 3 we outline the salient studies in these various fields.

## Epidemiological Studies

A number of prospective epidemiological studies have examined the relationship between levels of PA and subsequent depressive symptom development. Physical inactivity and lower fitness levels may increase the risk of depression, however other studies have found no

| Preventive approach | Definition and explanation | Clinical examples in for the field of physical activity in the treatment and prevention of depression |
|---|---|---|
| Universal [45] | Strategies that involve the whole population. Provided without screening. | Environmental design andmodification (e.g. green space development, walkway modification); cross-governmental initiatives; internet-based promotions; informational programs for the general public [44] |
| Selective [45] | Strategies that involve targeted subpopulations whose risk of developing a disorder is above average. Involves identified exposure to specific risk factors. | Risk factors for depression [69,88,89]:<br>• Pre-existing disease: e.g. psychiatric illness (e.g. anxiety disorder, age-related cognitive dysfunction, substance-related disorders); general medical conditions (e.g. cardiovascular disease, obesity, diabetes)<br>• Health related behaviors: e.g. psychological stress; physical inactivity; alcohol, tobacco and other drugs; sleep disruption; dietary factors.<br>• Biological factors: e.g. interferon therapy; pro-inflammatory conditions; S/S 5-HTTLPR genotype |
| Indicated [45] | Strategies aimed at subjects who have early and sub-threshold symptoms and signs of illness. Involves a screening process. | Sub-threshold depression; early intervention. |
| Primary [46] | Strategies to avoid occurrence of disease. | As per universal and selective approaches. |
| Secondary [46] | Strategies to diagnose and treat existent diseases in early stages before significant morbidity occur. | Relapse prevention; attenuation of episode duration and severity of episode; early intervention. |
| Tertiary [46] | Strategies to reduce negative impact of existent disease by restoring function and reducing disease-related complications. | Prevention of cognitive decline; prevention of psychotropic drug use and therefore reduced side effects; prevention of catatonia; prevention of adverse effects of illness on social and occupational functioning. |

**Table 1:** Clinical implications of preventive science frameworks in depression.

| Approach | Examples of study types and characteristics |
|---|---|
| Epidemiological | Cross-section analyses; prospective analyses. |
| Population-level intervention | Green-space modification; personal computer-based interventions; cross-governmental approaches; work place based interventions;<br>*Setting:* Whole population or sub-population. |
| Clinical trial | Randomized; placebo-controlled; blinded; pilot. |
| Psychological and sociological study | Qualitative and psychosocial analyses. |
| Clinical neuroscience | *Methodology*: Neuroimaging (e.g. structural and functional magnetic resonance imaging, positron emission tomography); serum and cerebral spinal fluid analyses.<br>*System*: Neuroimmunology; neuroplasticity; oxidative stress; neurotransmission; hypothalamopituitaryadrenal axis physiology; mitochondrial physiology. |
| Basic neuroscience | *Methodology*: cell culture; rodent studies; neuroimaging.<br>*System*: Neuroimmunology; neuroplasticity; oxidative stress; neurotransmission; hypothalamopituitaryadrenal axis physiology; mitochondrial physiology. |

**Table 2:** Approaches to examining the role of physical activity in the treatmentand prevention of depression.

association [10-18,47]. Interestingly, depression may increase the risk of physical inactivity [10,19,20]. An analysis of the 9,309 adult participant, Whitehall II prospective cohort study found the association between PA and depression appears to be bidirectional [10]. This analysis was conducted across 8 years, over 3 time points and utilized a self-administered questionnaire to determine PA levels. Participants were 35 to 55 years at baseline, in 1985. A cross-sectional inverse association between PA and depressive symptoms was found at baseline (OR 0.72). In cumulative analyses, regular PA across all three data waves, but not irregular PA, was associated with reduced likelihood of depressive symptoms at follow up (OR 0.71). In a converse analysis, participants with anxiety and depressive symptoms at baseline had higher odds of not meeting the recommended levels of PA at follow up (OR 1.79). A study by Dishman et al. examined longitudinal change in Cardiorespiratory

| Ref. | Objective | Study design | Demographic, participant data | PA measure | Depression measure | Results |
|---|---|---|---|---|---|---|
| [10] | To examine the bidirectional association between PA and depression/anxiety using data on physical activity and symptoms of anxiety and depression at three points in time over 8 years | British Whitehall II prospective cohort study<br>Data at baseline (phase 1; 1985), phase 2 (1989-1990), phase 3 (1991-1993). | 9,309 participants<br>Baseline: 35-55 yrs. Civil servants.<br>Men 6 374. | Self-administered questionnaire. @ phase 1, 2, 3. | 30-item GHQ @ phase 1, 2, 3.<br>Depression: 4 or more. | Cross-sectional: Inverse association btw PA and depressive sxs at baseline (OR 0.72)<br>Prospective: Reg PA, not irreg PA, α reduced likelihood of depressive sxs at f/u (OR 0.71).<br>Depressive and anxiety sxs at baseline α higher odds of not meeting recommended levels of PA at f/u (OR 1.79) |
| [12] | To examine longitudinal change in cardiorespiratory fitness, an objective marker of habitual physical activity, and incident depression complaints made to a physician | Aerobics Center Longitudinal Study. Subjects were included who did not complain of depression at their first clinic visit in 1971-2003 | Cardiorespiratory fitness assessed at four clinic visits between 1971 and 2006. Each separated by an average of 2-3 years. 7936 men and 1261 women, aged 20-85 years. | Cardiorespiratory fitness: total time of a symptom-limited maximal treadmill exercise test, using a modified Balke protocol. | Depression complaints were obtained from archived physician charts by the medical staff after follow-up to patient responses on a standardized medical history questionnaire | Across subsequent visits, there were 446 incident cases in men and 153 cases in women.<br>After adjustment for age, time between visits, BMI at each visit, and fitness at Visit 1, each 1-minute decline in treadmill endurance (i.e., a decline in cardiorespiratory fitness of approximately 1 half-MET) between ages 51 and 55 years in men and ages 53 and 56 years in women, increased the odds of incident depression complaints by approximately 2% and 9.5%, respectively. |
| [15] | To compare the effects of higher levels of physical activity on prevalent and incident depression with and without exclusion of disabled subjects. | Population-based prospective cohort study.<br>Followed up for 5 yrs | 1,947 community-dwelling adults from the Alameda County Study aged 50–94 years at baseline in 1994. | PA was measured with an eight-point scale. PA scale based on four questions | DSM–12D based on DSM-4. | Greater physical activity was protective for both prevalent depression (adjusted odds ratio (OR)=0.90) and incident depression (adjusted OR = 0.83) over 5 years. Exclusion of disabled subjects did not attenuate the incidence results (adjusted OR = 0.79). |
| [18] | The objective of this study was to follow individuals over time to examine whether those with higher levels of CRF have lower risk of developing depressive symptoms | Prospective cohort study.<br>Average of 12 years of follow-up | 11,258 men and 3085 women enrolled in the Aerobics Center Longitudinal Study | Participants completed a maximal treadmill exercise test at baseline (1970-1995) and a follow-up health survey in 1990 and/or 1995.<br>CRF was quantified by exercise test duration | 20-item CES-D | 282 women and 740 men reported depressive symptoms.<br>The odds of reporting depressive symptoms were 31% lower for men with moderate CRF (OR 0.69) and 51% lower for men with high CRF (OR 0.49), compared to men with low CRF. Corresponding ORs for women were 0.56 and 0.46. |
| Clinical trial evidence | | | | | | |
| [53] | To determine if a pragmatic aerobic exercise intervention would have antidepressant properties in a group of clinically depressed patient's. | RCT. Single centre, two-armed, parallel-group, observer-blinded randomized clinical superiority trial. Outpatients with major depression (DSM-IV) were allocated to supervised aerobic or stretching exercise groups during a three months period. | Mean age in the enrolled group was 41.6 years56 participants were allocated to the aerobic exercise intervention versus 59 participants to the stretching exercise group. | 56 participants were allocated to the aerobic exercise intervention versus 59 participants to the stretching exercise group. | HAM-D17 | Post intervention the mean difference between groups was −0.78 points on the HAM-D17 (95% CI −3.2 to 1.6; P=.52). Due to lower recruitment than anticipated, the trial was terminated prior to reaching the pre-defined sample size of 212 participants; therefore the results should be interpreted in that context. |
| [52] | To assess the benefit and harm of exercise training in adults with clinical depression. | Randomized, parallel-group, observer blinded clinical trial | Criteria for unipolar depression and were aged between 18 and 55 years | Patients (N = 165) were allocated to supervised strength, aerobic, or relaxation training during a 4-month period | HAM-D(17) | At 4 months, the mean change in HAM-D(17) score was -1.3 (-3.7 to 1.2; p = 0.3) and 0.4 (-2.0 to 2.9; p = 0.3) for the strength and aerobic groups versus the relaxation group. At 12 months, the mean differences in HAM-D(17) score were -0.2 (-2.7 to 2.3; p = 0.8) and 0.6 (-1.9 to 3.1; p = 0.6) for the strength and aerobic groups versus the relaxation group. |

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| [31] | Whether a mind-body exercise, Tai Chi Chih (TCC), added to escitalopram will augment the treatment of geriatric depression designed to achieve symptomatic remission | RCT. 14-week follow-up | 112 older adults with major depression age 60 years and older were recruited and treated with escitalopramfor approx. 4 weeks. Seventy-three partial responders to escitalopram continued to receive escitalopram daily and were randomly assigned to 10 weeks of adjunct use of either 1) TCC for 2 hours per week or 2) health education (HE) for 2 hours per week. | TCC. TCC sessions were held for a duration of 2 hours, once a week. Each TCC class was conducted in 120 minutes and also included 10 minutes of warm-up (e.g., stretching and breathing) and 5 minutes of cooldown exercises. | HDRS | Subjects in the escitalopram and TCC condition were more likely to show greater reduction of depressive symptoms and to achieve a depression remission as compared with those receiving escitalopram and HE. |
| [56] | To assess the effectiveness of an aerobic exercise program compared with standard medication (ie, antidepressants) for treatment of MDD in older patients. | RCT. 16-weeks | One hundred fifty-six men and women with MDD (age, > or = 50 years) were assigned randomly to a program of aerobic exercise, antidepressants (sertraline hydrochloride), or combined exercise and medication | 16 week aerobic exercise intervention. Subjects attended 3 supervised exercise sessions per week for 16 consecutive weeks. Participants were assigned individual training ranges equivalent to 70% to 85% of heart rate reservecalculated from the maximum heart rate achieved during the treadmill test. Each aerobic session began with a 10-minute warm-up exercise period followed by 30 minutes of continuous walking or jogging at an intensity that would maintain heart rate within the assigned training range. | HAM-D, BDI, DSM-IV | After 16 weeks of treatment, the groups did not differ statistically on HAM-D or BDI scores; adjustment for baseline levels of depression yielded an essentially identical result. Growth curve models revealed that all groups exhibited statistically and clinically significant reductions on HAM-D and BDI scores. However, patients receiving medication alone exhibited the fastest initial response; among patients receiving combination therapy, those with less severe depressive symptoms initially showed a more rapid response than those with initially more severe depressive symptoms. |
| [57] | The purpose of this study was to assess the status of subjects with MDD 6 months after completion of a study in which they were randomly assigned to a 4-month course of aerobic exercise, sertraline therapy, or a combination of exercise and sertraline. | RCT. | 156 adult volunteers. 4-month course of aerobic exercise, sertraline therapy, or a combination of exercise and sertraline. | Three supervised exercise sessions per week for 16 consecutive weeks. Participants were assigned training ranges equivalent to 70% to 85% of heart rate reserve. Each aerobic session began with a 10-minute warm-up period, followed by 30 minutes of continuous cycle ergometry or brisk walking/jogging. | HRSD. BDI. Assessments were performed at baseline, after 4 months of treatment, and 6 months after treatment was concluded | At 4 months: patients in all three groups exhibited significant improvement; the proportion of remitted participants (i.e, those who no longer met diagnostic criteria for MDD and had an HRSD score <8) was comparable across the three treatment conditions. At 10-months: remitted subjects in the exercise group had significantly lower relapse rates than subjects in the medication group. Exercising on one's own during the follow-up period was associated with a reduced probability of depression diagnosis at the end of that period (OR = 0.49). |
| Clinical immunological evidence | | | | | | |
| [65] | To examine the extent to which inflammatory markers can be used to predict response to exercise treatment after an incomplete response to an SSRI. To examine how the inflammatory markers change with exercise and if those changes are associated with dose of exercise or changes in symptom severity. | Prospective. Randomised. TREAD study. Participants had MDD and were partial responders to an SSRI (i.e. ≥14 HRSD-17 following >6 wks but <6 mnths of treatment). Excluded if regularly engaging in PA Age 18 – 70 yrs 73 participants 12-week | Randomized to either 16 or 4 KWW Aerobic EXC (treadmill or cycle ergometers). Combination of supervised and home-based sessions. | Clinician: IDS-C30 Self-rated: IDS-SR30 and HRSD17 | ELISA of serum at baseline and 12 weeks. IFN-γ, IL-1β, IL-6, TNF-α | High baseline TNF-α (>5.493 pg ml) α greater ↓ in depression sxs (IDS-C) over 12 wks Sig pos α between Δ IL-1β and Δ depression sxs. For 16KKW not 4 KKW. NS change in cytokine levels following 12 wks of EXC. NS relationship between EXC dose and change in cytokine levels. High TNF-α may predict better outcomes with EXC vs. SSRI ↓ IL-1β α positive depression treatment outcomes |

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|---|---|---|---|---|---|---|
| [61] | To determine if a long-term exercise intervention among older adults would reduce serum inflammatory cytokines, and if this reduction would be mediated, in part, by improvements in psychosocial factors and/or by β-adrenergic receptor mechanisms. | Adults ≥64 yrs.<br>Community-based.<br><br>Randomised to aerobic or flexibility/strength EXC. 10 months.<br>A subgroup of patients on non-selective β1β2-adrenergic antagonists were included. | Aerobic (CARDIO) or flexibility/strength EXC (FLEX).<br>3 d/wk, 45 min/day, 10 months. | GDS, PSS, CS, SPS, LOT | ELISA of plasma: CRP, IL-6, TNF-α, IL-18 | EXC = ↓ depressive symptoms, ↑ optimism (CARDIO = FLEX)<br>CARDIO EXC = ↓IL-6, IL-18, CRP, TNF-α vs. FLEX<br>FLEX EXC = ↓ TNF-α, no change in IL-6, IL-18, CRP vs. CARDIO.<br>↓ CRP α ↓ depressive symptoms<br>No effect for non-selective β1β2-adrenergic antagonists |
| [67] | To evaluate the effects of a behavioral intervention, TCC on circulating markers of inflammation in older adults. | 83 healthy older adults (59 – 86 yrs)<br><br>RCT. 2 arms – TCC, HE.<br>16 wk intervention + 9 wks follow up | TCC and HE.<br>Groups of 7 to 10.<br>TCC 20 mins, 3/wk. | BDI<br>PSQI | ELISA of plasma for IL-6, CRP, sIL-1ra, sIL-6, sICAM, IL-18<br><br>**high IL-6 >2.46 pg/ml* | High IL-6 at entry: TCC ↓ IL-6 comparable to those in TCC and HE who had low IL-6 at entry. IL-6 in HE remained higher than TCC and HE with low entry IL-6<br>TCC ns Δ cellular markers of inflammation<br>TCC = ↓ depressive sxs α ↓ IL-6 |

PA: Physical Activity; GHQ: General Health Questionaire; yrs: years; reg: regular; irreg: irregular; OR: Odds Ratio; MET:Metabolic Equivalent; DSM: Diagnostic and Statistical Manual; CRF: cardiorespiratory fitness; HAM-D: Hamilton Depression Rating Scale; MDD:Major Depressive Disorder; TCC: Tai Chi Chih; HE: Health Education; BDI: Beck Depression Inventory; IDS: Inventory of Depressive Symptoms; KKW: kilocalories per kilogram per week; IL: InterLeukin; TNF:Tumour Necrosis Factor; CRP: C-Reactive Protein; RCT:Randomized Controlled Trial

**Table 3:** Selected studies examining the role of physical activity in the prevention and treatment of depression.

Fitness (CRF) and incident depression complaints made to a physician [12]. This study assessed CRF at four clinic visits between 1971 and 2006 in 7936 men and 1261 women, aged 20-85 years. Subjects did not have depression at baseline. During subsequent visits there were 446 incident cases of depression in men and 153 cases in women. It was found that each 1-minute decline in treadmill endurance (i.e. decline in CRF of 1 half-MET) between ages 51 and 55 years in men and 53 and 56 years in women increased the odds of incident depression by approximately 2% and 9.5%, respectively. Therefore, maintenance of CRF during late middle age, when decline in CRF usually accelerates, helps protect against the onset of depression. Another study by Strawbridge et al. has compared the effects of higher levels of PA on prevalent and incident depression [15]. This study examined 1947 community-dwelling adults from the Alameda County Study aged 50-94 years at baseline in 1994 with 5 years of follow-up. Greater PA was protective for both prevalent depression (OR 0.90) and incident depression (OR 0.83) over 5 years. In a study of younger adults, Suija et al. examined a study population consisting of 5497 males and females of 31 years of age [18]. CRF was measured by 4-min step test and muscle fitness by tests of maximal isometric handgrip and trunk extension. They found lower levels of isometric endurance capacity of trunk extensor muscles were associated with high levels of depressive symptoms in both sexes. In males poor handgrip strength was associated with increased levels of depressive symptoms. There was no association between CRF and depressive symptoms.

## Clinical Trial Evidence

A number of primary research, meta-analyses and systematic reviews have examined the efficacy of various subtypes of PA in depression [26,34,29-32,48-54]. Two recent Cochrane Database meta-analyses examining PA effects in depression treatment suggests mixed and resistance PA are more effective than aerobic exercise [26,55]. The most recent meta-analysis by Cooney et al. examined 3 studies with mixed PA, 28 with aerobic PA and 4 with resistance type, with 1352 participants in total [55]. The standardized mean differences (SMD) for aerobic PA indicated a moderate clinical effect (SMD -0.55, 95% CI -0.77 to -0.34), whilst the SMDs for both mixed PA(SMD -0.85, 95% CI -1.85 to 0.15) and resistance PA(SMD -1.03, 95% CI -1.52 to -0.53) indicated large effect sizes, but confidence intervals were wide. When all 35 studies (1356 participants) comparing exercise with no treatment or a control intervention are examined, the pooled SMD at the end of treatment was -0.62 (95% CI -0.81 to -0.42), indicating a moderate clinical effect. There was moderate heterogeneity ($I^2$=63%). Importantly, however, when only 6 methodologically robust trials with 464 participants are included (i.e. with adequate allocation concealment, intention-to-treat analysis and blinded outcome assessment) the pooled SMD was not significant (-0.18, 95% CI -0.47 to 0.11). An RCT by Blumenthal et al. compared the efficacy of aerobic exercise, an antidepressant (sertraline) or combination for 16 weeks [56]. This study involved older subjects with MDD and found no significant different in efficacy between PA and sertraline. Sertraline produced the fastest initial response. A 6-month follow up analysis of this study by Babyak et al. found the exercise group had lower relapse rates as compared to the antidepressant group [57]. Other randomized-controlled trials suggest there is no difference between aerobic vs. stretching, aerobic vs. strength vs. relaxation training on depressive symptoms, however these studies are limited by diagnostic heterogeneity and variability in PA program design [52,53,58]. A meta-analysis of 4 trials and 253 participants examined the effectiveness of tai chi in reducing depressive symptoms among older adults. All four studies compared tai chi to waiting list control group. The pooled SMD was -0.27 (95% CI -0.52 to -0.02, P=0.03). Further research was recommended by the study author with larger sample sizes, more clarity on trial design, intervention and longer-term follow up. A recent RCT found tai chi was effective in augmenting escitalopram in the treatment of geriatric depression [31]. A 12-week pilot study has examined the short-term efficacy of exer-games (entertaining video games that combine game play with exercise) for sub-syndromal depression in 19 older adults [35]. The subjects utilized exer-gaming for three 35-minute sessions a week and a significant improvement in depressive symptoms was found (measured by the Quick Inventory of Depressive Symptoms – Clinician Rated Version). The abovementioned evidence suggests there are some anti-depressive effects for various subtypes of PA, however, methodological heterogeneity makes these studies difficult to compare and there are no studies comparing aerobic, resistance and mind-body PA in a randomized, controlled setting.

Rethorst and Trivedi have recently released guidelines for the treatment of MDD, based on a review of available literature [54]. These guidelines suggest for patients with MDD, aerobic or resistance training should be considered, 3-4 exercise sessions/week, for 45 - 60 minutes,

for at least 10 weeks and with an intensity of 50-60% of maximal heart rate. Of course, these guidelines should be modified according to individual patient-related factors.

## Clinical Immunological Evidence

Clinical neuroscience evidence in this field can be examined from a number of neurobiological perspectives [21,24,59,60]. Systems include neurotransmission, neuroplasticity, neuroimmunology, the Hypothalamopituitary Adrenal (HPA) axis, oxidative stress and mitochondrial physiology [21,24,59,60]. The effects of PA will be outlined below, with a specific focus on immune effects.

PA appears to exert significant effects on the immune system in depression. A clinical trial by Kohut et al. randomized 87 healthy older adults (64 to 87 years) to either aerobic (CARDIO) or strength and flexibility (FLEX) training 3 days/week, 45 min/day for 10 months [61]. A subgroup of subjects treated with non-selective $\beta_1$ and $\beta_2$ adrenergic antagonists were included to evaluate the potential role of β-adrenergic receptor adaptations as mediators of PA-induced change in inflammation. The study found CARDIO treatment resulted in significant reductions in serum CRP, IL-6 and IL-18 compared to FLEX treatment, whereas TNF-α declined in both groups. However, both groups had similar improvements with depressive symptoms (measured by the Geriatric Depression Scale (GDS)). This may be explained by emerging literature suggesting both beneficial and detrimental effects of pro-inflammatory cytokines, depending on their environmental milieu (outlined extensively in another review [62]). We have previously suggested that these beneficial and detrimental effects of PICs and other immune factors are in a state of balance, and that differing PA subtypes may exert variable effects on this balance [21]. For example, TNF-α has been found to exert detrimental and anti-neuroplastic effects via TNF-R1/p55, whereas TNF-R2/p75 has been found to exert beneficial and pro-neuroplastic effects [62-64]. A recent study by Rethorst et al. investigated the extent to which inflammatory markers can be used to predict response to exercise treatment after an incomplete response to a Selective Serotonin Reuptake Inhibitor (SSRI) [65]. This study randomized 73 participants aged 18 to 70 years to 12 weeks of either 4 or 16 kilocalories per Kilogram of Body Weight per Week (KWW), via aerobic PA. The study examined serum IFN-γ, IL-1β, IL-6, TNF-α and made a number of interesting findings. High baseline TNF-α (>5.493 pg/ml) was associated with a greater reduction in depressive symptoms (measured by Inventory for Depressive Symptomatology Clinical (IDS-C)). There was also a significant correlation between reductions of IL-1β and depressive symptoms in the 16 KWW group, but not the 4 KWW group. Otherwise, there was no significant change in cytokine levels following the 12 week PA intervention, and a non-significant association between PA dose and change in cytokine levels. A cross-sectional study by the same authors, Rethorst et al., examined the relationship between IL-6 and depressive symptoms by participation in moderate-intensity PA in a sample of 97 primary care patients aged > 40 years [66]. The patients had a Center for Epidemiological Studies Depression (CES-D) scale of > 15 and PA was determined by a questionnaire. In this study, there was no correlation between IL-6 and depressive symptoms and no effect for PA on IL-6 levels; however, the association between IL-6 and depressive symptoms was moderated by PA. In physically inactive subjects, higher depressive symptoms were associated with higher IL-6 levels. An RCT by Irwin et al. investigated the effects of Tai Chi Chih(TCC) on inflammatory markers (IL-6, CRP, sIL-1ra, sIL-6, sICAM, IL-18), as compared to control (Health Education (HE)) [67]. This study involved 83 healthy older adults (aged 59-86) in a 16 week intervention with 9 week follow up. This study found subjects with high IL-6 at entry (>2.46 pg/ml) had TCC-induced reductions in IL-6 to levels comparable to those found in TCC and HE subgroups who have low levels of IL-6 at baseline, whereas IL-6 levels in HE remained higher than the TCC and HE subgroups with low baseline IL-6. Reductions in depressive symptoms in the two groups correlated with decreases of IL-6. TCC did not affect other inflammatory markers.

A recent study may assist in correlating epidemiological and neuroscience findings in this area. A prospective cohort study based on participants from the Whitehall II study has found regular PA is associated with lower markers of inflammation over 10 years of follow-up [68]. This is important given the clinical and pre-clinical findings that depression may be precipitated by a pro-inflammatory state [69,70]. The study by Hamer et al. utilized 4289 men and women (mean age 49.2 years) and attained self-reported PA and inflammatory markers (hsCRP and IL-6) at baseline (1991) and follow up (2002) [68]. Higher PA levels over 10 years were associated with lower CRP and IL-6 levels as compared to lower PA levels. This study suggests that high-adherence to PA guidelines may be important in preventing the pro-inflammatory state seen with physical inactivity, as well as depression [68].

PA is found to enhance 5-HT, HA and DA signaling [21,24,59,60]. PA has been found to induce ROS formation leading to an up-regulation in endogenous antioxidant defenses, increased anti-oxidant/oxidative damage-repairing enzyme activity, increased resistance to oxidative stress and lowered levels of oxidative damage [21,24,59,60]. Long-term PA is shown to improve HPA axis responsiveness [21,24,59,60]. For example, PA has recently been found to reduce rumination (chronic stress) related increases in cortisol [71]. HPA axis hyperactivity has been repeatedly shown in depressed subjects, and is thought to be due to reduce glucocorticoid receptor functioning leading to glucocorticoid insensitivity [39,72]. PA is associated with enhanced adult HC neurogenesis and increased activity-dependent synaptic plasticity [21,24,59,60]. A recent review by Voelcker-Rehage and Niemann compares the clinical effect of 'metabolic exercise' (i.e. cardiovascular and resistance training) and co-ordinative PA (i.e. motor fitness, co-ordination and flexibility) on cognitive function in aging and markers of neuroplasticity [73]. The authors present evidence arguing pure metabolic PA has greater effects on brain volume and functional activity, particularly in the prefrontal and Hippocampal (HC) areas, as compared to stretching, toning or relaxation interventions (for primary evidence see); they contribute this effect to differing metabolic demands [73-76]. How this relates to studies in depression is unclear.

## Discussion

The rise in burden of depression, physical inactivity and metabolic syndrome make the case for developing innovative, PA-related strategies in the prevention of depression compelling [1,2,6,7]. Developing an integrated understanding of PA-related strategies from public health, clinical and neuroscience perspectives is important given the complex nature of this issue. Figure 1 provides a graphical representation of the multiple facets involved in preventive science approaches using PA as a preventive and treatment strategy for depression.

PA has shown positive effects in the treatment and prevention of depression and this data comes from epidemiological, clinical, psychological and neuroscience perspectives. A review of the epidemiological literature suggests higher levels of PA and Cardio-Respiratory Fitness (CRF) are associated with lower levels of depressive symptoms, lower incidence of depression and lower inflammation levels [10-18]. Clinical trials suggest that aerobic, resistance and mind-body

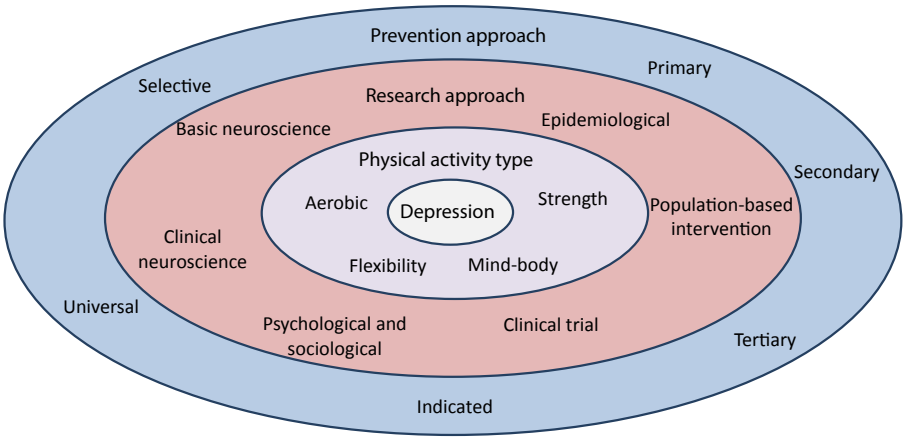


**Figure 1:** Schema for further exploring the role of physical activity in the treatment and prevention of depression
The figure outlines the importance of considering physical activity subtypes, as well as the type of research and preventive approach.

PA types may be therapeutic in the treatment of sub-syndromal and major depression, as well as relapse prevention [26,34,29-32,48-53].

Emerging evidence suggests there may be unique biological profiles of PA subtypes, and a greater understanding of these profiles may assist in increasing PA efficacy by personalizing treatment approaches. From an immune perspective, the RCT by Kohut et al. suggests aerobic treatment resulted in significant reductions in serum CRP, IL-6 and IL-18 compared to strength and flexibility treatment, whereas TNF-α declined in both groups [61]. Another study compared resistance and aerobic exercise in sedentary adults and found resistance PA produced a greater reduction in CRP than aerobic PA, 32.8% vs. 16.1%, respectively [77]. Although these first studies are suggestive of distinct PA subtype specific immunological changes, it is difficult to draw firm conclusions on the specific immunomodulatory profiles for these PA subtypes at this stage of the research given the small number of comparative studies and methodological heterogeneity between studies (e.g. study population age and illness severity. Biological factors which may underlie immunomodulatory and neuroplastic profiles of PA subtypes include specific effects on adipose tissue, muscle, blood vessels, vagal tone and the brain [77-80].

Immune markers may be moderators of the treatment efficacy of various treatment approaches. Aerobic PA is shown to be more efficacious with subjects (partial responders to SSRIs) who have a higher baseline TNF-α (>5.493 pg/ml) [65]. This finding may suggest TNF-α as a moderator between SSRI and exercise treatment, and TNF-α levels could be used to recommend exercise rather than medication as part of a personalized treatment algorithm [65]. Eller et al. found high baseline TNF-α associated with non-response to an SSRI, and the Hannestad et al. meta-analysis also supports this association [81,82]. The RCT by Irwin et al.found subjects which high IL-6 at entry (>2.46 pg/mL) have greater reductions in IL-6 and depressive symptoms than control [67]. The magnitude of this reduction was similar to aerobic PA [83].

It is important to acknowledge the psycho-social benefits of PA in the treatment and prevention of depression. Studies have shown exercise regimens have a distraction effect (from negative thoughts and ruminations), provide a sense of mastery via the learning of new skills, and hence enhance self-efficacy and self-esteem [84-86]. Additionally, exercise regimens in a group setting may have a beneficial effect via training social skill deficits [26]. The social training aspects of PA may be a confounder when assessing the biological effects of PA. Social isolation stress is repeatedly shown to enhance inflammation in clinical and pre-clinical models [87].

## Conclusion

The investigation of the preventive effects of PA on depression is a rapidly developing, important field. This paper summarizes the most recent evidence from public health, clinical and immunological studies which taken together support a role for PA in the treatment and prevention of depression. This paper proposes an integrated approach to this field in order to enhance the efficacy of preventive measures in the future.

## Conflict of Interest

All authors declare that there are no conflicts of interest

## Competing Interests

There are no competing interests

## Author's Contributions

HE conceived of the review and drafted the manuscript. KS and BB made substantial contributions to review design, analysis, interpretation and critically revision of data and the manuscript. All authors read and approved the final manuscripts.

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