

PERSPECTIVE IN REHABILITATION

Exercise therapy improves both mental and physical health in patients with major depression

Jan Knapen^{1,2,3}, Davy Vancampfort^{1,4}, Yves Moriën³, and Yannick Marchal^{2,5}

¹Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium, ²Huis voor Chronische Zorg, Sint-Truiden, Belgium, ³AZERTIE, Zonhoven, Belgium, ⁴Department of Psychomotor Therapy, University Psychiatric Centre KU Leuven, Campus Kortenberg, Kortenberg, Belgium, and ⁵Department of Family Medicine and Chronic Care, Vrije Universiteit Brussel, Brussels, Belgium

Abstract

Purpose: to present clinical guidelines for exercise therapy in depressed patients derived from recent meta-analyses. **Method:** four meta-analyses on effects of physical exercise on mental and physical in depression were analysed. **Results:** For mild to moderate depression the effect of exercise may be comparable to antidepressant medication and psychotherapy; for severe depression exercise seems to be a valuable complementary therapy to the traditional treatments. Depression is associated with a high incidence of co-morbid somatic illnesses, especially cardiovascular diseases, type 2 diabetes and metabolic syndrome. Exercise is extremely powerful in preventing and treating these diseases. Physical exercise is an outstanding opportunity for the treatment of patients who have a mix of mental and physical health problems. Exercise therapy also improves body image, patient's coping strategies with stress, quality of life and independence in activities of daily living in older adults. **Conclusions:** Physical therapists should be aware, that several characteristics of major depression (e.g. loss of interest, motivation and energy, generalised fatigue, a low self-worth and self-confidence, fear to move, and psychosomatic complaints) and physical health problems interfere with participation in exercise. Therefore, motivational strategies should be incorporated in exercise interventions to enhance the patients' motivation and adherence in exercise programs.

Keywords

Depressive disorder, metabolic syndrome, physical therapy

History

Received 11 March 2014
Revised 24 September 2014
Accepted 30 September 2014
Published online 24 October 2014

► Implications for Rehabilitation

- For mild to moderate depression, the effect of exercise may be comparable with antidepressant medication and psychotherapy; for severe depression, exercise seems to be a valuable complementary therapy to the traditional treatments.
- Exercise therapy also improves physical health, body image, patient's coping strategies with stress, quality of life, and independence in activities of daily living in older adults.
- Motivational strategies should be incorporated in exercise interventions to enhance the patients' motivation.

Description of major depression

Depression refers to a wide range of mental health problems characterized by the absence of a positive effect (a loss of interest and enjoyment in ordinary things and experiences), persistent low mood, and a range of associated emotional, cognitive, physical, and behavioral symptoms [1]. Severity of depression is classified using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria as mild (five or more symptoms with minor functional impairment), moderate (symptoms or functional impairment are between "mild" and "severe"), and severe

(most symptoms present and interfere with functioning, with or without psychotic symptoms) [2].

Major depression consists of at least one 2-week major depressive episode [2]. The primary symptom of a major depressive episode is either depressed mood or loss of interest or pleasure. Additionally, the symptoms must not be clearly attributable to another medical condition or to the physiological effects of a substance. The symptoms cannot be better explained by a range of psychotic, schizophrenic, or delusional disorders. A major depressive episode is not diagnosed if there has ever been a manic or hypomanic episode. Symptoms that are clearly attributable to another medical condition are not counted in the required five symptoms minimum. Additionally, as with most psychiatric conditions, the symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The following is an

abbreviated summary of DSM-V symptoms of depression (at least five are needed for at least 2 weeks for a diagnosis of major depressive episode). With the exception of suicidal ideation and weight change, symptoms must be present most of the day, nearly every day.

Depressed mood most of the day and nearly every day

- Markedly diminished interest or pleasure, in all, or almost all, activities most of the day, nearly every day.
- Significant weight loss or gain when not dieting (i.e. 5% in a month), or decreased appetite nearly every day. Failure to make appropriate weight gains is considered in children.
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day.
- Diminished ability to think or concentrate or indecisiveness nearly every day.
- Recurrent thoughts of death, recurrent suicidal ideation without plan, or a suicide attempt or plan.

Major depression, a big public health problem

Recent epidemiological surveys conducted in general populations have found that the lifetime prevalence of depression is in the range of 10–15% [3]. Mood disorders, as defined by the World Mental Health and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, have a 12-month prevalence which varies from 3% in Japan to over 9% in the US [4]. A recent American survey found the prevalence of current depression to be 9% and the rate of current major depression to be 3.4% [5]. Several studies of depressive disorders have stressed the importance of the mortality and morbidity associated with depression [3,6]. The mortality risk for suicide in depressed patients is more than 20-fold greater than in the general population. Studies have also shown the importance of depression as a risk factor for cardiovascular death [7–10]. Greater severity of depressive symptoms has been found to be associated with significantly higher risk of all-cause mortality including cardiovascular death and stroke. Depression increases the risk of decreased workplace productivity and absenteeism resulting in lowered income or unemployment.

An analysis of data from the National Co-morbidity Survey Replication, a US nationally representative household survey, found that overall impairment was significantly higher for mental disorders than for chronic medical disorders [11]. Severe functional impairment was reported by 42% persons with mental disorders and 24% with chronic medical disorders. Treatment, however, was provided for a significantly lower proportion of mental (21.4%) than chronic medical (58.2%) disorders.

DALY, disability adjusted life-years, is the sum of life-years lost due to premature death and years lived with disability adjusted for severity [12]. It integrates the notions of individual mortality and disability with global disease prevalence. Using the DALY, unipolar major depression was classed in 2004, as the third leading burden of disease or injury cause worldwide for both sexes, behind lower respiratory infections and diarrheal diseases [12]. Worldwide projections by the World Health Organization for the year 2030 identify major depression as the leading cause of disease burden.

The substantial burden of major depression is due, in part, to the limited accessibility and effectiveness of treatments, with data indicating that only 55% of those with a depressive disorder seek treatment and only 32% receive an efficacious treatment (psychotherapy or antidepressant medication) [3]. Physical

exercise has been suggested as an efficient complementary treatment to reduce symptoms of depression since it reduces cost with drugs and hospitalizations, and may also improve physical health and physiological stress responses [13,14]. There are several hypotheses regarding the physiological and psychological mechanisms by which exercise impacts on mental health, such as enhancement of the synthesis and liberation of neurotrophic factors, as well as of cognitive functioning, angiogenesis, neurogenesis, and plasticity. Moreover, some studies have shown that physical exercise may improve physical and global self-esteem, quality of life, coping strategies with stress, and social contact [15]. Furthermore, it may also contribute to increased quality of life and independence in activities of daily living in older adults [14].

Physical exercise as intervention for depression: findings of two recent meta-analyses

A recent meta-analysis of the Cochrane Collaboration investigated the effectiveness of exercise in the treatment of depression in adults compared with no treatment or a comparator intervention [13].

This meta-analysis aimed to answer the following questions:

- Is exercise more effective than no therapy for reducing symptoms of depression?
- Is exercise more effective than antidepressant medication for reducing symptoms of depression?
- Is exercise more effective than psychological therapies or other non-medical treatments for depression?
- How acceptable to patients is exercise as a treatment for depression?

Which studies were included in the review?

The Cochrane research group used search databases to find all high-quality randomized controlled trials of how effective exercise is for treating depression in adults over 18 years of age. The authors searched for studies published up until March 2013. All studies had to include adults with a diagnosis of depression, and the physical activity carried out had to fit criteria to ensure that it met with a definition of ‘‘exercise’’. Thirty-nine studies with a total of 2326 participants were included in the systematic review.

What does the evidence from this review tell us?

The authors concluded that exercise is moderately more effective than no therapy for reducing symptoms of depression. In addition, exercise is no more or less effective than antidepressants for reducing symptoms of depression, although this conclusion is based on a small number of studies. Exercise is also no more or less effective than psychological therapies for reducing symptoms of depression, although this conclusion is based on a small number of studies. An important observation was that attendance rates for exercise treatments ranged from 50% to 100%.

Suggestions for further research

The authors recommend that future research should look into detail at what types of exercise could benefit people with depression most. Research should also investigate the optimal dose–response relationship. Further larger trials are needed to compare the effects of exercise therapy with antidepressants or psychological treatments.

Another very recent meta-analysis of 2013 evaluated the effect of aerobic and strength training as a treatment for major depression, using various aspects such as remission and response to treatment, age, severity of depression, and type of exercise (aerobic training and strength training) [14].

The following data were collected: total number of patients, age, randomized design, diagnostic criteria, assessment instruments, and the percentage of remission and treatment response. The outcome variables were proportion of remission (no symptoms) and at least 50% reduction of initial depression scores (response).

The authors concluded that physical exercise moderately reduces depressive symptoms in major depression patients (SMD = 0.61). Physical exercise is an efficient alternative treatment for depression with a 49% increase in the probability of response to treatment defined as a 50% reduction in initial depression scores. Individuals over 60 years of age showed a higher efficacy than those found in studies with populations below 60 years.

Patients with mild depressive symptoms showed a better treatment response than patients with mild/moderate depressive symptoms. Aerobic training was more effective than strength training. In this meta-analysis, the efficacy of exercise in the treatment of depression was influenced by age and symptom severity. It is reasonable that physical exercise may in some cases be considered an alternative to antidepressants for the treatment of mild major depression in older persons. This finding might contribute to decreasing the use of medication and hospitalization and in promoting independence in activities of daily living in elderly patients. An important limitation of this meta-analysis is, however, that the samples of all studies included consisted of patients with mild or moderate depression.

Major depression and metabolic syndrome

Depressed persons have approximately a two-fold increased risk of having or developing cardiovascular disease [7–10]. Further, after a cardiovascular event, the risk of onset of depression is increased, resulting in poorer cardiovascular outcome. The metabolic syndrome, a constellation of cardiovascular risk factors including (abdominal) obesity, hypertension, dyslipidemia and hyperglycemia, has been suggested to be one possible pathway linking depression and cardiovascular disease.

A recent meta-analysis clearly demonstrated that metabolic syndrome occurs frequently in depressed persons [16]. The authors included 18 publications ($n = 5531$) with clearly defined major depression, all published between 2004 and June 2013. They reported that 30.5% of individuals with major depression suffered from metabolic syndrome. The relative risk for metabolic syndrome was 1.5 times higher for persons with depression compared with general population controls.

Consistent with population studies, the research group found no significant difference between men and women, indicating that both sexes need the same attention and care. In addition, age also did not explain differences in prevalence estimates, indicating that the high risk for metabolic abnormalities should be a concern across the lifespan. However, antipsychotic drugs use significantly ($p < 0.05$) explained higher metabolic syndrome prevalence estimates in patients with major depression.

Another meta-analysis on the bidirectional association between depression and metabolic syndrome concluded that metabolic syndrome is an independent risk factor major depression [17]. Individuals with metabolic syndrome have a higher relative risk to develop clinically diagnosed depression (OR = 2.18) than individuals without metabolic syndrome.

The positive bi-directional longitudinal association between depression and metabolic syndrome means that depression is causing metabolic syndrome and vice versa. This association suggests a possible pathophysiologic overlap [17]. More specifically, elevated cortisol secretion due to hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, (pro)-inflammatory

processes, oxidative stress, autonomic nervous system dysregulation, and insulin resistance are all interacting biological mechanisms that may mediate the association between depression and metabolic syndrome. Although biological processes might be important, background lifestyle, and socioeconomic factors are probably equally relevant [16]. For example, major depression increased the odds for developing hyperglycemia and hypertriglyceridemia, which could be due to depression or related changes in diet and exercise, but which clearly increases the risk for metabolic syndrome.

Conclusion: both major depression and metabolic syndrome are associated with increased mortality and morbidity, possibly through the association with various medical diseases such as cardiovascular disease and diabetes mellitus type 2. Unhealthy lifestyles such as poor diet and lack of physical activity are suggested to be mediating the association between major depression and metabolic syndrome.

The role of lifestyle factors

Poor diet, physical inactivity, and smoking have long been recognized as key contributors to the high prevalence non-communicable diseases, such as cardiovascular disease, type 2 diabetes, metabolic syndrome, and cancer. However, there are now an increasing number of studies suggesting that the same modifiable lifestyle behaviors are also risk factors for common mental disorders, such as major depression. Research on major depression has confirmed that it is caused by an array of biopsychosocial and lifestyle factors [18]. Diet and lack of physical exercise are two such influences that play a significant mediating role in the development, progression, and treatment of this condition. Poor diet and physical inactivity can influence several physiological pathways associated with depression.

Growing evidence indicates a role for physical inactivity as a risk factor for major depression, while exercise has been shown to be effective in treatment studies [13,14]. There is some evidence that smoking is highly prevalent among mental disorders. Diet quality is the most recent area of attention in the lifestyle mental health research field. A recent review found consistent evidence that severity of obesity is associated with the relationship between obesity and depression, such that having a BMI that falls within the class III obese category may confer risk of co-morbid depression [19]. Given that a greater severity of obesity is associated with greater health risks and physical impairment aligns with research that has found higher levels of physical impairment and lower levels of quality of life to be associated with depression [20]. Thus, it seems likely that severity of obesity may be an important risk factor in determining an individual's risk of developing co-morbid depression.

While these lifestyle factors are significant in the etiology and maintenance of depression, a multitude of other factors influences may also be important [18]. These include chronic stress, social influences, mental, and physical effects associated with medical diseases, alcohol and other drug use, chronic pain, and even exposure to sunlight/vitamin D. They are these influences in combination with a large array of psychological, genetic, and biological factors that often complicate the treatment of depression. Basic interventions comprising attention towards one cause and/or one biochemical mechanism (e.g. targeting a single neurotransmitter disturbance) makes the goal of remission or recovery less likely. This was highlighted in a recent study where giving simple written recommendations about lifestyle changes for sleep hygiene, physical activity, diet, and sunlight exposure in addition to antidepressant treatment enhanced compared with standard antidepressant treatment alone [21]. Remission/response

rates reached 60% in the combined treatment group compared with 10% in the anti-depressant only group.

It might be hypothesized that lifestyle changes will not only have beneficial mental health benefits in persons with major depression. Since both depressive symptoms and metabolic syndrome appear to have a two-directional relationship, poor diet and lower physical activity levels might partially mediate the association between depression and metabolic syndrome. When both conditions are present, additional metabolic disturbances might promote a chronic character of the depressive symptoms. These are suggestive of a vicious cycle and are indicative of the existence of a specific condition, which might be labeled as metabolic depression [18]. Lifestyle interventions for depressed patients might improve both mental and somatic health status and could possibly prevent mechanisms that may mediate the association between depression and metabolic syndrome [17,22].

Conclusion: physical exercise and diet have an impact on both physical and mental health, and desirable changes in these lifestyle factors can be useful in the prevention and treatment of depression and metabolic syndrome.

Evidence-based recommendations for exercise therapy in patients with depression

In this last section, we offer some general recommendations for physical fitness assessment and exercise prescription, for inventorying perceived barriers and benefits towards exercise participation and propose some strategies for improving patient's motivation and adherence to an exercise programme.

Physical fitness assessment and exercise prescription

Developing an exercise prescription for people with depression differs from the prescription used for healthy individuals. Physical therapists should be aware that several characteristics of major depression (e.g. loss of interest, motivation and energy, generalized fatigue, a low self-worth and self-confidence, fear to move, and psychosomatic complaints) and physical health problems interfere with participation in exercise.

Designing well-considered exercise programs for these patients requires (1) a risk stratification for patients with comorbid somatic disease, (2) an assessment of physical fitness and the perceived exertion during exercise, and (3) an inventory of the perceived barriers and benefits towards exercise participation.

Risk stratification for patients with co-morbid somatic disease

Before initial treatment, physical therapists should identify high-risk individuals, such as patients with a history of cardiovascular disease or diabetes [23]. These patients should be medically cleared before beginning physical activity. For the vast majority of people, the risk of sudden cardiac events is, however, minimal, as long as they start at a realistic pace. Low-intensity physical activity is related to a low risk. For example, a walking program at light to moderate intensity is safe for most patients. Intensity can be increased over time, and the patient and physical therapist should pay attention to symptoms such as chest pain or shortness of breath. Besides, the moderate training stimulus should be adapted to the training status and side effects of psychotropic medication (such as constipation, dizziness, dry mouth, nausea, sweating, and tremor) [23].

Assessment of physical fitness and the perceived exertion during exercise

Direct measurement of maximal oxygen intake by way of a maximal exercise test is the most accurate indicator of cardio-respiratory fitness [23]. Maximal tests, however, have the

disadvantage of requiring the subject's optimal motivation to work to 'near exhaustion', and require the supervision of a physician and the use of expensive equipment. For depressed and anxious patients, however, submaximal measures are highly recommended for the reasons that many patients have poor physical health, low levels of fitness and physical self-worth, few experience with aerobic training, and less energy and motivation for heavy physical effort [24,25]. Salmon pointed out that, especially in this population, physiological measurements studied in a laboratory could be influenced due to pre-test anxiety [26]. Patients with an increased trait/state anxiety, for example, might fear that maximal aerobic effort will provoke physiological reactions such as hyperventilation, tachycardia, dizziness, or sweating, which they associate with symptoms of panic attacks [27]. These clinical considerations usually lead to the application of submaximal exercise tests in psychiatric settings. At the University Psychiatric Centre KU Leuven, Campus Sint-Jozef Kortenberg, the 6-min walk test [28] and the Franz ergocycle test [24] are most commonly used.

For patients with major depression who often suffer from fatigue and low motivation, the rate of perceived exertion during physical activity is an important parameter when designing an appropriate exercise schedule [24,25]. The fatigue and recovery time following an effort are not only dependent on physiological stressors (intensity, duration, and frequency of the training stimulus) but also on psychosocial factors. Psychological and social problems cause considerable stress. Generalized fatigue and lack of energy are typical symptoms of major depression. The exercise tolerance of patients is reduced due to the fact that they are preoccupied with physiological reactions during effort such as palpitations, perspiration, and hyperventilation. These psychological factors cannot be ignored when developing a well-designed fitness program. The evaluation of degree of perceived exertion can be derived from the psychophysiological concept of Borg [29]. The Borg 15 Graded Category Scale and the Borg Category Ratio 10 Scale quantify the sensations that the subject experiences during physical effort. The Borg 15 Graded Category Scale has a score range from 6 to 20 (15 grades), and the Borg Category Ratio 10 Scale from 0 to 10 (10 grades). Both scales show a linear relationship with heart rate during progressive incrementally exercise ($r = 0.94$ and $r = 0.88$, respectively). At the University Psychiatric Centre KU Leuven, Campus Sint-Jozef Kortenberg, we use the Borg Category Ratio 10 Scale because the longer Borg 15 Graded Category Scale requires a greater differentiation capacity.

Inventorying perceived barriers and benefits towards exercise participation

Depressed patients accumulate a lot of barriers for participation in exercise such as psychosomatic complaints, a low self-worth and self-confidence, loss of energy, interest and motivation, generalized fatigue, weak physical fitness and health condition, fear to move, overweight and a low feeling of personal control concerning own fitness and health, and helplessness and hopelessness [15,25]. Consequently, it is highly recommended to have a conversation concerning barriers and possible strategies that assist a patient in overcoming these barriers (e.g. problem solving, planning activity, seeking social support) before starting an exercise program. Furthermore, giving information regarding both mental and physical health benefits of regular physical activity and determining which benefits are most salient to each patient is essential. For inventorying of perceived barriers and benefits physical therapists may use a decision balance that patients helps to reflect the relative weighing of the pros and cons of exercise participation [30].

Strategies for improving motivation and adherence to exercise

Strategies could be based on the principles of Motivational Interviewing following Miller and Rollnick [31], and the Transtheoretical Model of Behaviour Change [30,32]. This model postulates that exercise behaviour change involves progress through six stages of change: pre-contemplation, contemplation, preparation, action, maintenance, and termination.

Initial phase: starting with supervised exercise

- Create exercise programs based on the patient's current preferences and expectations, the initial physical fitness assessment and the measurement of perceived exertion during exercise.
- Draw up an individual plan with the patient taking into account emotional, cognitive, and physiological components of major depression.
- Help the patient set realistic and achievable goals which lead to success experiences; this generally gives courage to persevere.
- Adapt the moderate exercise stimulus to the individual's health status and physical abilities, age, training status and exercise history, expectations and goals, side effects of psychotropic medication, exercise tolerance, and perceived exertion.
- Follow the program with exercise cards and a logbook and provide regular progress feedback to the patients.
- Avoid between-patient comparisons.
- Emphasize the short-term benefits after single exercise sessions: improvements in mood and state anxiety, stress level, energy level, distraction of negative thoughts, the ability to concentrate and focus, and quality of sleep. Many patients are focused on the distant outcomes, such as weight loss and improved self-worth, so emphasizing short-term benefits can help patients adhere exercise participation.
- Empathy, validation, praise, and encouragement are necessary during all phases but especially when patients struggle with ambivalence and doubt their ability to accomplish the change.

Second phase: maintaining supervised exercise

- Focus on perceived fitness gains, achievement of personal goals, mastery experiences, and sense of control over the body and its functioning.
- Use cognitive-behavioral strategies such as self-monitoring, stimulus cuing, goal-setting, and contracting.
- Once patients begin to feel better as a result of exercise, they are eager to continue their exercise if the therapist can help them attribute their improved mood to the exercise regimen. Improved mood as a result of increased physical activity may be obvious to the therapist, but the connection is not always obvious to the patient. Exercise can give patients a sense of power over their recovery, which in itself counteracts the feelings of hopelessness often experienced in depression.
- Self-determined motivation towards exercise is very important and results in adaptive exercise-related behaviors, cognitions, and physical self-evaluations. Therefore, it is important to make physical activity as self-determined as possible by focusing on the positive experiences of the activity itself, as well as helping to develop an identity of a physical active person.

Third phase: follow-up after supervised exercise

- Follow-up contact is very important: discuss problem solving around barriers, reinforce all progress toward change (even if

initially very small progress), and encourage modification of goals as needed.

- Seek support of others such as family and friends.
- Use relapse behaviors/strategies: it is important to explain to patients that relapses are part of the process of change, and that responding with guilt, frustration, and self-criticism may decrease their ability to maintain physical activity. Relapse prevention strategies such as realistic goals setting, planned activity, realistic expectations, identifying and modifying negative thinking, and focusing on benefits of single exercise sessions seem to be effective.

Conclusion

Two recent meta-analyses confirm that exercise is an effective treatment for depression. For mild to moderate depression, the effect of exercise may be comparable with antidepressant medication and psychotherapy; for severe depression, exercise seems to be a valuable complementary therapy to the traditional treatments. Exercise therapy also improves physical health (e.g. metabolic syndrome), body image, patient's coping strategies with stress, quality of life, and independence in activities of daily living in older adults. Motivational strategies should be incorporated in exercise interventions to enhance both the patients' motivation and their long-term adherence to exercise, taking into account emotional, cognitive, and physiological components of depression.

Declaration of interest

The authors report that there are no declaration of interest.

References

1. National Institute for Health and Clinical Excellence. Depression: the treatment and management of depression in adults (update). London: National Institute for Health and Clinical Excellence; 2009.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
3. Lépine J, Briley M. The increasing burden of depression. *Neuropsychiatr Dis Treat* 2011;7:3–7.
4. Demyttenaere K, Bruffaerts R, Posada-Villa J, et al. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. *JAMA* 2004;291:2581–90.
5. Centers for Disease Control and Prevention. Current depression among adults – United States, 2006 and 2008. *Morb Mortal Wkly Rep* 2010;59:1229–35.
6. Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry* 2001;58:844–50.
7. Whang W, Kubzansky LD, Kawachi I, et al. Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses' Health Study. *J Am Coll Cardiol* 2009;53:950–8.
8. Lett H, Blumenthal J, Babyak M, et al. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom Med* 2004;66:305–15.
9. Penninx BW, Beekman AT, Honig A, et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry* 2001;58:221–7.
10. Rugulies R. Depression as a predictor for coronary heart disease. A review and meta-analysis. *Am J Prev Med* 2002;23:51–61.
11. Druss BG, Hwang I, Petukhova M, et al. Impairment in role functioning in mental and chronic medical disorders in the United States: results from the National Comorbidity Survey Replication. *Mol Psychiatry* 2009;14:728–37.
12. World Health Organization. The global burden of disease: 2004 update. Geneva: World Health Organization Press; 2004.
13. Cooney GM, Dwan K, Greig CA, et al. Exercise for depression. *Cochrane Database of Systematic Reviews* 2013, Issue 9. Oxford: Cochrane Collaboration 2013.

14. Silveira H, Moraes H, Oliveira N, et al. Physical exercise and clinically depressed patients: a systematic review and meta-analysis. *Neuropsychobiology* 2013;67:61–8.
15. Knapen J, Van de Vliet P, Van Coppenolle H, et al. Comparison of changes in physical self-concept, global self-esteem, depression and anxiety following two different psychomotor therapy programs in non-psychotic psychiatric inpatients. *Psychother Psychosom* 2005; 74:353–61.
16. Vancampfort D, Correll C, Wampers M, et al. Metabolic syndrome and metabolic abnormalities in patients with major depressive disorder: a meta-analysis of prevalences and moderating variables. *Psychol Med* 2013;21:1–12.
17. Pan A, Keum N, Okereke O, et al. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes Care* 2012;35: 1171–80.
18. Lopresti AL, Hood SD, Drummond PD. A review of lifestyle factors that contribute to important pathways associated with major depression: diet, sleep and exercise. *J Affect Disord* 2013;148:12–27.
19. Preiss K, Brennan L, Clarke D. Obesity comorbidity: a systematic review of variables associated with the relationship between obesity and depression. *Obes Rev* 2013;14:906–18.
20. Guh DP, Zhang W, Bansback N, et al. The incidence of comorbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health* 2009;25:88.
21. Garcia-Toro M, Ibarra O, Gili M, et al. Four hygienic-dietary recommendations as add-on treatment in depression: a randomized-controlled trial. *J Affect Disord* 2012;140:200–3.
22. Zoeller R. Physical activity: depression, anxiety, physical activity, and cardiovascular disease: what's the connection? *Am J Lifestyle Med* 2007;1:175–80.
23. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 8th ed. Baltimore: Lippincott Williams & Wilkins; 2010.
24. Knapen J, Van de Vliet P, Van Coppenolle H, et al. Evaluation of cardio-respiratory fitness and perceived exertion for patients with depressive and anxiety disorders: a study on reliability. *Disabil Rehabil* 2003;25:1312–15.
25. Knapen J, Van de Vliet P, Van Coppenolle H, et al. Improvements in physical fitness of non-psychotic psychiatric patients following psychomotor therapy programs. *J Sports Med Phys Fitness* 2003;43: 513–22.
26. Salmon P. Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. *Clin Psychol Rev* 2001;21: 33–61.
27. Ströhle A, Graetz B, Scheel M, et al. The acute antipanic and anxiolytic activity of aerobic exercise in patients with panic disorder and healthy control subjects. *J Psychiatr Res* 2009;43: 1013–17.
28. Vancampfort D, Probst M, Maurissen K, et al. Reliability, minimal detectable changes, practice effects and correlates of the six-minute walk test in patients with schizophrenia. *Psychiatry Res* 2011;187: 62–7.
29. Borg G. Borg's perceived exertion and pain scales. Champaign, IL: Human Kinetics; 1998.
30. Marshall S, Biddle S. The transtheoretical model of behavior change: a meta-analysis of applications to physical activity and exercise. *Ann Behav Med* 2001;23:229–46.
31. Miller W, Rollnick S. Motivational interviewing: preparing people for change. New York: Guilford Press; 2002.
32. Prochaska J, Velicer W. The transtheoretical model of health behavior changes. *Am J Health Promot* 1997;12:38–45.