

Healthy lifestyle interventions in general practice: Part 12: Lifestyle and depression

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Introduction

This article forms part 12 of the series on the role of lifestyle modification in general practice with specific reference to patients with depression. "Depression" is a term often used to describe an entire spectrum of mental health problems, ranging from dysphoria of mood (feeling down), to a clinical disorder such as a major depressive disorder (MDD).¹ MDD is characterised by periods of depressed mood and/or loss of interest or pleasure that lasts at least two weeks. These symptoms are accompanied by a number of somatic symptoms (including changes in sleep, libido, energy and vigour, appetite and psychomotor function) as well as cognitive symptoms (including feelings of worthlessness, concentration or decision making difficulty, poor concentration and suicidal thoughts) that cause clinically significant distress or impairment of everyday functionality.¹

According to the World Health Organization mental health disorders are common and affect one in four individuals (24%) at some time in their life.² Although prevalence may vary from country to country, the overall prevalence of depression is approximately 10%. Depression is one of the leading causes of disability worldwide and is predicted to be the second largest contributor to the global burden of disease by the year 2020.³

Data for prevalence rates of major depressive disorders in South Africa are limited. The most recent cross-sectional prevalence study, the SA Stress and Health study⁴ estimated the lifetime prevalence of major depressive episode at 9.7%.⁵ The prevalence was 1.75 times greater in females compared to males and 2.11 times more common in those with a low level of education (Grade 1–7) than with higher levels of education. The mean age of onset was 25.8 years, and over 90% of respondents with depression reported global role impairment.⁵

Depression is commonly managed with antidepressant medication and psychotherapy, but some patients and practitioners may prefer alternative or additional lifestyle-based strategies including exercise therapy, dietary

modification or other psychosocial interventions. This review will focus on these three forms of lifestyle interventions.

I. Physical exercise

Physical activity in patients with depression

It has long been well established that there is a meaningful relationship between physical exercise and mood states. A significant negative relationship exists between levels of physical activity and the prevalence of depression; and conversely, physical inactivity is associated with an increased risk and prevalence of depression.⁶⁻⁹ However, it is difficult to determine causality from these cross-sectional studies as depression per se might attenuate the desire to exercise. Thus it is important to consider data from longitudinal and intervention studies.

When these studies are evaluated, there is a large and increasing body of evidence that supports the use of physical exercise as a treatment strategy for patients with depression.¹⁰⁻¹⁶ This effect is prevalent even in older populations¹⁷ and in patients with postpartum depression. Indeed, symptom reduction following exercise training occurs in both patients with diagnosis of MDD and in patients with subclinical mood disorders (dysthymia).

Whilst most meta-analyses and reviews have concluded a clinically significant and strong effect of exercise intervention in depression, a recent comprehensive and stringent Cochrane review has concluded that, whilst exercise training seems to improve depressive symptoms in individuals with a diagnosis of depression, more methodologically robust trials are required to obtain accurate estimates of effect sizes and determine accurate risks and costs.¹⁴ However, all reviews and studies to date advocate that it is reasonable to recommend exercise training, together with other interventions, to individuals with depressive symptoms who fulfill the diagnostic criteria for depression. In fact, in some trials, the antidepressant effect size of exercise training can be comparable to that of either psychotherapy or pharmacotherapy.^{10;17-19} Exercise training in combination with

pharmacological agents might even result in more rapid onset of antidepressant action; indeed, it is interesting to postulate that exercise training in combination with pharmacological agents and the other lifestyle interventions mentioned in this article might have further positive synergistic effect on mood.

Preliminary studies on the effective dose of exercise have shown that the public health recommendations as published by the American College of Sports Medicine and described in the first publication of this series, is effective in the management of patients with depression.²⁰

Physiological benefits of physical exercise in depressed patients

Whilst the physiological neurobiological effects of exercise training on mood stabilisation and elevation are not fully understood, the following effects have been described:

- Endogenous opioids, including the endorphins and enkephalins or endogenous cannabinoids which cause relative euphoria, are released after vigorous physical activity.²⁰⁻²²
- The neurotransmitters serotonin, norepinephrine, dopamine and concentrations of the serotonin precursor tryptophan are thought to be positively influenced by exercise training.²³⁻²⁸
- Exercise training is thought to positively regulate disorders of the hypothalamic pituitary axis which may be present in chronic stress and depression.²⁹
- Exercise has been shown to increase concentrations of the neurotrophins, brain derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF) which regulate the wellbeing of neuronal tissue (neurogenesis) rather than the neurotransmitters.^{30,31}
- Exercise training may induce favourable alterations in anterior cingulate prefrontal cortex activity similar to that induced by the antidepressant agents.³²

Furthermore the following beneficial physical and psychosocial effects are known to occur through exercise training:

- Improved joint range of motion, increase in cardiovascular function, muscle strength and endurance capacity.
- Improved body composition, sleep, quality of life, self-efficacy (mastery), improved fitness, and functional capacity with respect to activities of daily living.
- A modest reduction of fatigue, enhanced body image and sense of control is achieved.
- Other benefits of regular physical activity include a reduction in other risk factors for chronic cardiac disease including hypertension, hyperlipidaemia, obesity and diabetes.

Practical considerations in prescribing exercise for patients with depression

- Psychological barriers including fear, perceived lack of knowledge and previous negative experiences with exercise may inhibit participation in exercise. Therefore a well-structured, individualised, supervised exercise training programme is recommended.

- Symptoms including fatigue, reduced pleasure, and feelings of worthlessness may make exercise more challenging compared to people without these symptoms. Thus compliance with exercise training might pose a problem. Therefore, realistic achievement goals should be set with the patient at the initiation of an exercise programme. For example, overweight or obese patients who are depressed should be counselled to focus on improved mood rather than on weight loss as a goal of exercise training.
- Patients should be monitored and encouraged as small milestones are achieved, as this practice may lead to a sense of mastery and confidence, which in turn may enhance compliance with the exercise programme.
- The social interaction with an exercising group or an exercise trainer might also positively encourage depressed patients to continue with their exercise routines.
- Some anti-depressant medication might induce fatigue and interfere with exercise tolerance and training. Studies performed in this laboratory have indicated that some of the tri- and tetracyclic antidepressants, as well as the serotonin re-uptake inhibitor ritanserin, decrease muscle power output during high intensity cycling exercise. Thus, clinicians should be aware that these agents might have an adverse effect on exercise tolerance and alternative medications might be prescribed which may be devoid of these effects.

II. Psychosocial interventions

While there is a dearth of mental health professionals available in many contexts in South Africa, and GPs themselves often have neither the time nor the training to offer psychological intervention at primary health level, it remains an important clinical challenge facing general practitioners whether to prioritise pharmacological or psychological treatment. The evidence is strong that short-term (three months) psychological treatment is at least as effective as anti-depressant medication in mild-moderate depression, and should be considered when it is available, especially if patients have significant negative thinking and distorted self-perceptions.³³ For example, Keller et al, showed that pharmacotherapy and psychotherapy were equally effective in gaining response or remission in 52-55% of patients. Significantly, the combination of therapies was substantially more effective, with an 85% response rate.³⁴

The majority of studies comparing various forms of short-term (as opposed to long-term) individual psychotherapies for mild-moderate depression show no significant difference in effectiveness between major forms.³⁵ The psychological interventions available that practitioners might consider include:

- Cognitive behavioural therapy (CBT): CBT is aimed at evaluating, challenging, and modifying a patient's dysfunctional beliefs (cognitive restructuring).
- Brief psychodynamic therapy: Focus on developing

awareness and insight about repetitive conflicts (intrapsychic and intrapersonal), with the assumption that a patient's childhood experiences, past unresolved conflicts, and historical relationships significantly affect their present life situation.

- **Interpersonal psychotherapy:** Addresses interpersonal issues in depression to the exclusion of all other foci of clinical attention.
- **Problem-solving therapy:** Includes definition of personal problems, generation of multiple solutions to each problem, selection of the best solution, the working out of a systematic plan for this solution, and evaluation as to whether the solution has resolved the problem.
- **Nondirective supportive therapy:** Any unstructured therapy without specific psychological techniques other than those common to all approaches, such as helping people to ventilate their experiences and emotions and offering empathy.

It is important that practitioners are aware that many psychotherapists in South Africa offer long-term psychotherapy, lasting a number of years. This is predominantly psychoanalytically-orientated, the theoretical basis of which is similar to psychodynamic therapy referred to above.

One of the most encouraging and novel approaches to the management of depression has emerged over the last decade. Based on the practice of mindfulness meditation, Mindfulness-Based Cognitive Therapy (MBCT) is an eight week programme which has been consistently shown in randomised, multi-centred trials to reduce the relapse rate of major depression (three or more episodes) by 43%, independent of medication, and is maintained at 15 month follow up.^{36,37} The premise of this acceptance-based (as opposed to change-based) therapy is to observe without judgement the depressogenic thinking (i.e. negative self-beliefs such as 'I am worthless') which generate depressed mood. This decentering from the thinking mind breaks the vicious cycle between cognition and mood, as patients recognise that they are not their thoughts and that by simply watching them, rather than identifying with them as the truth, thoughts move through and evaporate of their own accord.

III. Dietary interventions

Dietary habits have the potential to influence health and disease across a spectrum of conditions, including mental health.^{38,39} Growing evidence supports the notion that dietary choices have an influence on mood states.³⁹ Furthermore, there is much interest in the use of nutrition modalities as therapeutic agents over and above their conventional role as a supply of energy.⁴⁰

Depression itself may have an effect on appetite (increased or decreased) and may result in the decline of nutrition status.³⁸ Thus nutritional management of depression relates not only to the body's ability to adequately produce neurotransmitters, but also to address certain environmental influences as

determinants of a depressed mood. Clinical management goals should therefore address those factors which could negatively impact dietary practices and nutritional status in depressed patients.

Unhealthy eating patterns

Research has demonstrated an association between depression and eating behaviour, including unhealthful eating practices, poorer food choices, unhealthful weight-control practices and binge eating.^{38,39,41} This association further includes an increased intake of carbohydrates, sugary and sweet foods, a higher energy intake, and a higher percentage of energy from fat.^{39,41-43} Indeed, chocolate has often been identified as having a pronounced effect on mood.³⁹ Depressive symptoms have also been associated with the reduced frequency of the consumption of vegetables and fruits in a sample of female first-year students.³⁸ This emphasises the importance of establishing healthful eating habits, particularly in young adults, as it holds implications for sustained healthy behaviour throughout adult life. Efforts to address depressive symptoms may beneficially impact dietary choices.

Foods and nutrients

Various macro and micronutrients have been suggested as having an influence on mood.³⁹

- **Carbohydrates:** The intake of 'comfort foods' is often stimulated by poor mood.³⁹ Meals containing a high carbohydrate content have been postulated as increasing serotonin synthesis, resulting in an enhanced mood. This theory, however, is unlikely to hold true, as only a small amount of protein (2–4% of energy) will negate this effect, more of which is contained in a typical meal.³⁹ It is uncertain whether those who are depressed consume more carbohydrates, or vice versa. Nevertheless, the consumption of carbohydrates has been hypothesised to relieve depressive moods in the short term.^{38,39} The mechanism for this remains unclear. Chocolate is often seen as a source of comfort, and suggestions around the mood-enhancing properties of chocolate relate to its constituents (anandamines, caffeine, phenylthylamine and magnesium). However, the concentration of these elements is too low to warrant them acting as drug-like constituents.³⁹ An elevated mood resulting from chocolate intake, instead, is associated with its palatability (taste and mouth-feel) which stimulates endorphin release.³⁹
- **Micronutrients:** Psychological symptoms have been associated with various vitamin deficiencies and changes in mood may be one of the first indications of sub-clinical micronutrient deficiencies.³⁹ However, little is known about the effect of micronutrient supplementation on mood. Due to their role in neurotransmitter synthesis and metabolism, it can be argued that there is a role of certain micronutrients in affecting mood. Evidence suggests a relationship between mood and folate status.⁴⁴ Depression

in the elderly has been associated with folate deficiency and improved mood has further been associated with improved thiamine status.³⁹ In women, iron deficiency anaemia is associated with depression, rapid fatigue and apathy when exercising.³⁹ Emerging evidence warrants further investigation of these associations before the prescription of micronutrient supplementation in depressed individuals is to be recommended.

- *Poly-unsaturated fatty acids*: Fatty acids are being widely recognised as playing an increasing important role in various disorders including heart disease, rheumatoid arthritis and various psychiatric disorders.⁴⁰ Existing evidence supports an association between omega-3 poly-unsaturated fatty acids (PUFAs) and depression.^{40,45,46} This finding seems consistent across study designs, groups and in a variety of populations, which has suggested a causal relationship.⁴⁵ The promising anti-depressive compounds are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In four double-blind placebo-controlled studies, treatment of EPA, alone or with DHA, was found to be more effective as opposed to a placebo in the treatment of patients with depression (who were taking concurrent antidepressants).⁴⁵ While depression itself may result in changes in the dietary intake or lipid concentrations of omega-3 PUFAs, it is suggested that low concentrations, caused either by altered metabolism or reduced dietary intake, may contribute to enhanced receptiveness to depression.⁴⁵ Outstanding research issues include the exact dosage (1–2 g/day of EPA has been found to be effective)⁴⁶ and duration required to obtain clinically significant results, possible side effects of long-term use (mild gastrointestinal side effects and fishy taste are reported short-term side effects), the relationship between the two active ingredients, EPA and DHA, the onset of therapeutic effect, whether they are to be used as monotherapy or as an adjunct to anti-depressant medication, evidence in pregnant and paediatric populations, and the exact mechanism whereby PUFAs alleviate depression.⁴⁶

Insulin resistance and the metabolic syndrome

It is proposed that central nervous system (CNS) activity is involved in the aetiology of the metabolic syndrome.⁴⁷ The metabolic syndrome has been associated with reduced function of the serotonergic system.⁴⁷ Research by Kinder et al (2004) established an elevated prevalence of the metabolic syndrome amongst women with depression, after controlling for various confounders.⁴⁸ Features of the serotonergic system in the brain, suggest its involvement in the metabolic syndrome, (e.g. it regulates aspects related to eating, locomotion, pain, etc).⁴⁷ Possible mechanisms for this association include the dysfunctional serotonergic pathway's effect on physical activity, eating habits and indirectly, obesity, insulin resistance, etc.⁴⁷ Further findings have suggested a metabolic characteristic in depressive

disorders, that of impaired glucose utilisation, resulting from insulin resistance (IR) and that the effective management of depressive disorders should include therapeutic targets for IR. Whether depression is the consequence, cause or a mere marker of the metabolic syndrome, the association holds vital clinical consequences.⁴⁸ A better understanding of the association between depression and the metabolic syndrome is needed in an attempt to reduce the prevalence and health consequences of the metabolic syndrome.

Practical dietary recommendations for patients with depression

- Lifestyle interventions aimed at optimal health and wellness includes the elements of maintaining a healthy body weight and the following of a healthy balanced diet.
- The practitioner should aim to improve the patient's overall quality of diet, by encouraging them to follow a balanced approach that will provide the nutrients needed to promote health and prevent disease. This includes consuming a diet rich in fruits and vegetables, legumes, whole grains, low fat or fat free dairy, lean proteins (including oily fish), nuts, seeds and other healthy fats and oils.
- Because depression is common in patients with the metabolic syndrome, practitioners should be cognisant of taking special care to assess psychological parameters in such patients, and to adjust treatment interventions to accommodate added challenges with which patients with depression may present. Further, assess individuals for the metabolic syndrome and apply appropriate dietary and lifestyle interventions.
- Although supplementation is warranted in certain instances for specific therapeutic uses, and may have a role to play as an adjunct to a healthy balanced diet, it is not a suitable substitute for overall improved diet quality in the short or long term and its use should always be overseen by a nutrition expert. Presently, blanket supplementation for general populations is not to be recommended.

Conclusion

This article has provided an overview of the basic lifestyle modifications to consider in the management of patients with depression. A holistic view with respect to exercise training, dietary modification, and psychosocial interventions alone or in combination with anti-depressant medications are all important in patient management. General practitioners and psychiatrists and psychologists should particularly be aware of the benefits of exercise and healthy nutritional interventions and assist their patients by suggesting adherence to accepted physical activity and nutritional guidelines. All patients should therefore be afforded the time and interest of their practitioners so that they may assist their patients in making well informed choices with respect to their lifestyle to promote health and mental wellbeing.

Reference

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. ed. Washington, DC: American Psychiatric Association; 1994.
- Sartorius N, Ustun TB, Costa e Silva JA, Goldberg D, Lecrubier Y, Ormel J et al. An international study of psychological problems in primary care. Preliminary report from the World Health Organization Collaborative Project on 'Psychological Problems in General Health Care'. *Arch Gen Psychiatry* 1993;50(10):819–824.
- Lopez AD, Murray CC. The global burden of disease, 1990–2020. *Nat Med* 1998;4(11):1241–1243.
- Tomlinson M, Grimsrud AT, Stein DJ, Williams DR, Myer L. The epidemiology of major depression in South Africa: results from the South African stress and health study. *S Afr Med J* 2009;99(5 Pt 2):367–373.
- Tomlinson M, Grimsrud AT, Stein DJ, Williams DR, Myer L. The epidemiology of major depression in South Africa: results from the South African stress and health study. *S Afr Med J* 2009;99(5 Pt 2):367–373.
- Galper DI, Trivedi MH, Barlow CE, Dunn AL, Kampert JB. Inverse association between physical inactivity and mental health in men and women. *Med Sci Sports Exerc* 2006;38(1):173–178.
- Goodwin RD. Association between physical activity and mental disorders among adults in the United States. *Prev Med* 2003;36(6):698–703.
- Stephens T. Physical activity and mental health in the United States and Canada: evidence from four population surveys. *Prev Med* 1988;17(1):35–47.
- Ross CE, Hayes D. Exercise and psychologic well-being in the community. *Am J Epidemiol* 1988;127(4):762–771.
- Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *BMJ* 2001;322(7289):763–767.
- Greer TL, Trivedi MH. Exercise in the treatment of depression. *Curr Psychiatry Rep* 2009;11(6):466–472.
- Barbour KA, Edenfield TM, Blumenthal JA. Exercise as a treatment for depression and other psychiatric disorders: a review. *J Cardiopulm Rehabil Prev* 2007;27(6):359–367.
- aan het RM, Collins KA, Fitterling HL. Physical exercise and depression. *Mt Sinai J Med* 2009;76(2):204–214.
- Mead GE, Morley W, Campbell P, Greig CA, McMurdo M, Lawlor DA. Exercise for depression. *Cochrane Database Syst Rev* 2009;(3):CD004366.
- Strohle A. Physical activity, exercise, depression and anxiety disorders. *J Neural Transm* 2009;116(6):777–784.
- Daley A. Exercise and depression: a review of reviews. *J Clin Psychol Med Settings* 2008;15(2):140–147.
- Blumenthal JA, Babyak MA, Moore KA, Craighead WE, Herman S, Khatri P et al. Effects of exercise training on older patients with major depression. *Arch Intern Med* 1999;159(19):2349–2356.
- North TC, McCullagh P, Tran ZV. Effect of exercise on depression. *Exerc Sport Sci Rev* 1990;18:379–415.
- Martinsen EW. Physical activity and depression: clinical experience. *Acta Psychiatr Scand Suppl* 1994;377:23–27.
- Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO. Exercise treatment for depression: efficacy and dose response. *Am J Prev Med* 2005;28(1):1–8.
- Morgan WP. Affective beneficence of vigorous physical activity. *Med Sci Sports Exerc* 1985;17(1):94–100.
- Dietrich A, McDaniel WF. Endocannabinoids and exercise. *Br J Sports Med* 2004;38(5):536–541.
- Chaouloff F. Physical exercise and brain monoamines: a review. *Acta Physiol Scand* 1989;137(1):1–13.
- Meeusen R, De MK. Exercise and brain neurotransmission. *Sports Med* 1995;20(3):160–188.
- Greenwood BN, Foley TE, Day HE, Burhans D, Brooks L, Campeau S et al. Wheel running alters serotonin (5-HT) transporter, 5-HT_{1A}, 5-HT_{1B}, and alpha 1b-adrenergic receptor mRNA in the rat raphe nuclei. *Biol Psychiatry* 2005;57(5):559–568.
- Glavin GB. Stress and brain noradrenaline: a review. *Neurosci Biobehav Rev* 1985;9(2):233–243.
- Dishman RK. Brain monoamines, exercise, and behavioral stress: animal models. *Med Sci Sports Exerc* 1997;29(1):63–74.
- Dishman RK, Renner KJ, White-Welkley JE, Burke KA, Bunnell BN. Treadmill exercise training augments brain norepinephrine response to familiar and novel stress. *Brain Res Bull* 2000;52(5):337–342.
- Stranahan AM, Lee K, Mattson MP. Central mechanisms of HPA axis regulation by voluntary exercise. *Neuromolecular Med* 2008;10(2):118–127.
- van PH. Neurogenesis and exercise: past and future directions. *Neuromolecular Med* 2008;10(2):128–140.
- Lucassen PJ, Meerlo P, Naylor AS, van Dam AM, Dayer AG, Fuchs E et al. Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: Implications for depression and antidepressant action. *Eur Neuropsychopharmacol* 2010;20(1):1–17.
- Prakash RS, Snook EM, Erickson KI, Colcombe SJ, Voss MW, Motl RW et al. Cardiorespiratory fitness: A predictor of cortical plasticity in multiple sclerosis. *Neuroimage* 2007;34(3):1238–1244.
- Bortolotti B, Menchetti M, Bellini F, Montaguti MB, Berardi D. Psychological interventions for major depression in primary care: a meta-analytic review of randomized controlled trials. *Gen Hosp Psychiatry* 2008;30(4):293–302.
- Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000;342(20):1462–1470.
- Cuijpers P, van SA, Andersson G, van OP. Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *J Consult Clin Psychol* 2008;76(6):909–922.
- Teasdale JD, Segal ZV, Williams JM, Ridgeway VA, Soulsby JM, Lau MA. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *J Consult Clin Psychol* 2000;68(4):615–623.
- Ma SH, Teasdale JD. Mindfulness-based cognitive therapy for depression: replication and exploration of differential relapse prevention effects. *J Consult Clin Psychol* 2004;72(1):31–40.
- Mikolajczyk RT, El AW, Maxwell AE. Food consumption frequency and perceived stress and depressive symptoms among students in three European countries. *Nutr J* 2009;8:31.
- Benton D, Donohoe RT. The effects of nutrients on mood. *Public Health Nutr* 1999;2(3A):403–409.
- Lee S, Gura KM, Kim S, Arsenault DA, Bistrian BR, Puder M. Current clinical applications of omega-6 and omega-3 fatty acids. *Nutr Clin Pract* 2006;21(4):323–341.
- Cohen JH, Kristal AR, Neumark-Sztainer D, Rock CL, Neuhouser ML. Psychological distress is associated with unhealthy dietary practices. *J Am Diet Assoc* 2002;102(5):699–703.
- Wurtman JJ. Carbohydrate craving, mood changes, and obesity. *J Clin Psychiatry* 1988;49 Suppl:37–39.
- Gershon MD. Review article: serotonin receptors and transporters – roles in normal and abnormal gastrointestinal motility. *Aliment Pharmacol Ther* 2004; 20 Suppl 7:3–14.
- Williams E, Stewart-Knox B, McConville C, Bradbury I, Armstrong NC, McNulty H. Folate status and mood: is there a relationship? *Public Health Nutr* 2008;11(2):118–123.
- Sontrop J, Campbell MK. Omega-3 polyunsaturated fatty acids and depression: a review of the evidence and a methodological critique. *Prev Med* 2006;42(1):4–13.
- Osher Y, Belmaker RH, Nemet B. Clinical trials of PUFAs in depression: State of the art. *World J Biol Psychiatry* 2006;7(4):223–230.
- Muldoon MF, Mackey RH, Williams KV, Korytkowski MT, Flory JD, Manuck SB. Low central nervous system serotonergic responsivity is associated with the metabolic syndrome and physical inactivity. *J Clin Endocrinol Metab* 2004;89(1):266–271.
- Kinder LS, Carnethon MR, Palaniappan LP, King AC, Fortmann SP. Depression and the metabolic syndrome in young adults: findings from the Third National Health and Nutrition Examination Survey. *Psychosom Med* 2004;66(3):316–322.