Journal of Affective Disorders 196 (2016) 20–31

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Development, acceptability and efficacy of a standardized healthy lifestyle intervention in recurrent depression

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ARTICLE INFO

Article history:
Received 1 September 2015
Received in revised form
15 January 2016
Accepted 6 February 2016
Available online 11 February 2016

Keywords:
Exercise
Depression
Maintenance
Sleep
Smoking
Eating

ABSTRACT

Background: Research evidence on the effects of integrated multifaceted lifestyle interventions for depression is scanty. The aim of the present study is to report on the development, acceptability and efficacy of a standardized healthy lifestyle intervention, including exercise, eating habits, sleep hygiene and smoking cessation in preventing relapses.

Methods: One hundred-sixty outpatients with recurrent unipolar depression or bipolar disorder were recruited after achieving full remission or recovery from the most recent depressive episode. Patients were randomized to 3-months of usual care or to an intervention aimed at promoting a healthy lifestyle (HLI), as an augmentation of pharmacological maintenance treatment. Usual care consisted of clinical management visits. At the end of the intervention, follow-up visits were scheduled at 3,6,9 and 12 months.

Results: During the intervention phase, 1 relapse occurred in the HLI group and 4 in the control group. Over the 12 months of follow-up, relapses were 5 in the HLI group and 16 in control group. Using an intent-to-treat approach, the overall percentage of relapses was 6/81 (7.4%) in the HLI group vs. 20/79 (25.3%) in the control group.. In a Kaplan-Meier survival analysis the risk of relapse was significantly lower in patients receiving the HLI intervention (log-rank test, $p=0.003$) over the 60 weeks of observation.

The majority of patients assigned to HLI adhered to the program, and were highly motivated throughout the intervention.

Limitations: The retention rate was low because patients were recruited during the maintenance phase and the 1-year follow-up was relatively short to detect a long-term effect of HLI.

Conclusions: The HLI program proved to be efficacious in preventing relapses. Given the absence of contraindications and its cost-effectiveness in routine practice, the use of HLI should be encouraged to promote the well-being of patients with recurrent depression.

1. Introduction

Research has shown that depressed and bipolar patients are less fit, have diminished physical work capacity and more physical health problems, which impact on the course of their mental disorder (Fagiolini et al., 2002, 2003; Wildes et al., 2006; Morgan, 1968; Martinsen et al., 1985, 1989).

Still, converging evidence indicates that exercise improves psychological functioning and well-being (Scully et al., 1998; Otto et al., 2007; Galper et al., 2006; Dunn et al., 2005, 2001) and preliminary evidence shows that exercise can be used as an augmentation strategy in depressed patients who achieve a partial response to the SSRI (Trivedi et al., 2011, 2006). As a result, exercise is now included in the American Psychiatric Association's treatment recommendations (Rethorst and Trivedi, 2013).

Physical activity is a natural reinforcement behavior, although the specific mechanisms by which exercise promotes an antidepressant effect are largely unknown. Studies on animal models of depression show that the upregulation of NPY and BDNF, leading to cell proliferation and neurogenesis, is the final common pathway of antidepressant drugs is that of running (Bjornebekk et al., 2006; Bjørnebekk et al., 2005; Brene et al., 2007; Russo-Neustadt et al., 2004, 2001, 2000, 1999; Russo-Neustadt and Chen, 2005; Chen and Russo-Neustadt, 2007; Dishman et al., 2006; Garza et al., 2004) and that running can alter the turnover of central noradrenaline (Dunn, 1996). Aerobic exercise seems to

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http://dx.doi.org/10.1016/j.jad.2016.02.034
0165-0327/

improve the dysfunction of the HPA axis and reduce depression scores in patients with fibromyalgia (Bonifazi et al., 2006), and also the balance between the sympathetic and parasympathetic control of the sinoatrial node, as shown by changes in heart rate variability (Buchheit and Gindre, 2006). In addition, there may be an indirect effect of exercise on mood mediated by improved fitness, blood pressure, reduced body weight and metabolic changes such as the reduction of abdominal obesity and insulin resistance.

Sleep alterations are essential aspects of mood disorders: insomnia and hypersomnia are in fact nuclear symptoms and diagnostic criteria for a depressive episode (American Psychiatric Association, 2000). Ninety percent of depressed patients complain about sleep disorders: most complains difficulty falling asleep, frequent awakenings or terminal insomnia (Almeida and Pfaff, 2005; Tsuno et al., 2005); a minor amount of patients (6–29%) complain instead of hypersomnia (Roberts, 2000); in particular it seems that the latter is more common in bipolar depression and seasonal depression (Saeed and Bruce, 1998).

It has been documented that the presence of a subjective sleep disturbance precedes by about five weeks a recurrence depressive episode (Perlis et al., 1997). Many authors have suggested that insomnia may even have a causal role in the onset of depression in patients with a first episode, and in the recurrence of depression in patients in remission (Breslau et al., 1996, Livingston et al., 1993; Chang et al., 1997; Ford and Kamerow, 1989; Morawetz, 2003; Dryman and Eaton, 1991; Mallon et al., 2000; Roberts et al., 2000; Vollrath et al., 1989; Weissman et al., 1997; Perlis et al., 2006). Even in the case of bipolar disorder, insomnia often precedes and maintains the manic episode and both insomnia that hypersomnia may precipitate and maintain the depressive episode (Goodwin and Jamison, 2007). So it is evident that insomnia is a risk factor for a poor prognosis of depression (Cole and Dendukuri, 2003; Perlis et al., 1997; Riemann and Voderholzer, 2003): as already mentioned insomnia precedes the onset and recurrence depressive in more than 40% of cases (Ohayon and Roth, 2003). In addition, the risk of developing major depression is significantly higher in patients who complain of insomnia (Breslau et al., 1996; Dryman and Eaton, 1991; Mallon et al., 2000; Weissman et al., 1997). These observations suggest that promoting physical activity and weight reduction if needed, and regularizing the sleep-wake cycle may be useful strategies to prevent the recurrence of depression.

Despite the documented benefits of physical activity or exercise, dietary modifications, adequate sleep and social interactions, and reduction of recreational substances (Sarris et al., 2014), these factors received little considerations in the treatment of depression, where medication and psychological interventions remain the first-line treatment. In particular, studies exploring the impact of lifestyle modification involving multiple lifestyle elements are scanty. To our knowledge, only two RCTs examined the effects of multicomponent lifestyle interventions in patients with mood disorders. In the first study, comparing the efficacy of four specific dietary-hygienic recommendations with four generic recommendations in 80 outpatients with non-seasonal depression, Garcia-Toro et al. (2012) reported a significantly better evolution of depressive symptoms in the active treatment group and a drop-out rate of 25% in each group at six months. In the second study (Frank et al., 2015), carried out in 122 overweight patients with bipolar-I disorder in remission, an integrated risk reduction intervention including a psychiatric treatment and assessment, medical monitoring and a healthy lifestyle program was compared with a control condition including psychiatric treatment and assessment. The experimental intervention resulted in a modest BMI reduction at six months (2.3% vs. 0.2% in the control group).

The aims of the present study are to assess the acceptability and the efficacy of a standardized healthy lifestyle intervention + pharmacotherapy, compared with usual care + pharmacotherapy, in preventing the relapses of depressive episodes in patients with recurrent depression or bipolar disorders. We expected that the proportion of relapses would be lower among patients assigned to the experimental intervention during the intervention period and during the 1-year follow-up period.

2. Methods

Patients were recruited between 2011 and 2014 at the Department of Molecular and Developmental Medicine, Division of Psychiatry, of the University of Siena. Forty-five (28%) participants were referred from the endocrinology/obesity center of Siena hospital.

Inclusion criteria were:

- age > 18
- a history of at least 2 depressive episodes, the most recent with an onset < 4 months
- a diagnosis of recurrent major depressive disorder or bipolar disorder
- remission or full recovery from the depressive episode
- ongoing pharmacological maintenance treatment
- willingness to sign a written informed consent.

Exclusion criteria were:

- being in an acute depressive episode
- unwillingness/inability to provide a written informed consent
- the presence of severe medical illness that would contraindicate participation in the healthy lifestyle program.

The study protocol was approved by the Ethics Committee of the University Hospital of Siena. All patients signed a written informed consent to participate in the study after receiving a description of the study procedures.

2.1. Assessments

Patients' diagnosis at baseline was determined using the Structured Clinical Interview for DSM-IV axis-I disorders (First et al., 2002). Other assessments evaluated the presence and severity of depressive and manic symptoms, functioning, quality of life and sleep. The assessment time points are reported in Table 1. Relapse was determined based on the scores > 4 on the Clinical Global Impressions Scale (CGI-S), and either the Patient Health Questionnaire (PHQ $-$ 9) > 14 [depressive relapse] or the Young Mania Rating Scale (YMRS) ≥ 7 [manic/mixed relapse], as measured during the visit or through the Longitudinal Interval Follow-up Evaluation (LIFE, Keller et al., 1987), if symptoms started before the visit, and was confirmed by a study clinician.

The Patient Health Questionnaire (PHQ-9, Kroenke et al., 2001) is a self-administered instrument, which scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day). The total score ranges from 0 to 27. In the validation study, a PHQ-9 score $>$ or $= 10$ had a sensitivity of 88% and a specificity of 88% for the diagnosis of major depression. PHQ-9 scores of $5-9$, $10-14$, $15-19$, and ≥ 20 represent mild, moderate, moderately severe, and severe depression, respectively. The PHQ-9 proved to have good construct and criterion validity.

The Work and Social Adjustment Scale (WSAS, Mundt et al., 2002) is a self-report scale that assesses daily functioning; it consists of five items exploring work functioning, home management, social leisure, private leisure and relationships on an eight-

Table 1
Study assessments.

	Screening	V1	Each visit	Follow-up visits at months 3,6, 9, 12
SCID-I, demographic form, treatment history	X			
Current pharmacological treatment	X	X	X	X
Dispensed drugs	X	X	X	X
Clinical Global Impressions Scale (CGI)	X	X	X	X
Young Mania Rating Scale (YMRS)	X	X	X	X
Longitudinal Interval Follow-up Evaluation (LIFE)		X		X
Medical assessments				
Fitness to physical exercise	X	If necessary	If necessary	If necessary
Physical examination	X			X*
ECG	X			X*
Blood tests**	X**			X**
Urine drug tests	X		If necessary	If necessary
Pregnancy test (women in fertile age)	X	If necessary	If necessary	If necessary
Medical assessments				
Waist circumference		X		X
Hips circumference				
Weight				
Height				
Systolic pressure		X		X
Diastolic pressure				
Heart rate				
Self-report measures				
PHQ-9	X	X	X	X
Short form survey (SF-12)		X		X
Work and social adjustment scale (WSAS)		X		X
Occupational status		X		X
Pittsburgh sleep quality index (PSQI)		X		X
Epworth sleepiness scale (ESS)		X		X
Self-report instruments (only HLI group)				
Paffenbarger physical activity questionnaire		X		X
HLI adherence questionnaire			X	X

* Medical history, electrocardiogram and physical examination are conducted at the screening and at the 12 months follow-up visit.
** Laboratory tests include: urine analysis, pregnancy test, hemocrome, electrolytes, antithyroid antibodies, serum uric acid, creatinine, SGPT, SGOT, gamma-glutamyl transferase, lipid profile, T4 (tiroxine), T3, TSH, glucose, fasting insulin and glycated hemoglobine.

point ordinal scale. The total score ranges from 0 to 40. A score from 11 to 20 denotes mild functional impairment, while a score higher than 20 denotes severe functional impairment. In the validation study, internal consistency was found to range from 0.70 to 0.94, and the test retest correlation was 0.73. Interactive voice response administration of this scale yielded correlations of 0.81 to 0.86 with clinician interviews. The WSAS correlation with severity of depression was 0.76. Scores were sensitive to patient differences, in terms of disorder severity and treatment-related change (Mundt et al., 2002).

The Young Mania Rating Scale (YMRS, Young et al., 1978) includes 11 items and is used to assess disease severity in patients already diagnosed with mania. It is intended to be administered by a trained clinician who assigns a severity rating on a Likert scale for each item based on a personal interview. The total score ranges from 0 to 56. The scale is based on the patient's subjective report of his/her clinical condition over the previous 48 hours that typically takes 15–30 min to administer. Items can be rated by querying the patients or from direct observation, and encompass elevated mood, increased motor activity, sexual interest, sleep, irritability, speech, language/thought disorder, content, disruptive/aggressive behavior, appearance and insight. It is the most used outcome measurement in clinical trials and longitudinal naturalistic studies. The cut-off of ≥ 20 on the total YMRS score was used to define acute mania and a cut-off of ≥ 10 was used to define a manic/hypomanic switch in patients with unipolar depression (Rucci et al., 2013).

The Clinical Global Impressions Scale (CGI, Guy, 1976) provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. The CGI actually comprises two companion one-item measures. The CGI-S evaluates the severity of psychopathology from 1 to 7: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients. The CGI-I measures change from the initiation of treatment on a similar seven-point scale (1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from the initiation of treatment; 5=minimally worse; 6=much worse; 7=very much worse since the initiation of treatment. For the purposes of the present paper, we dichotomized the original CGI-I score by contrasting the first three categories (improved) vs. the other four (not improved).

The PSQI (Buysse et al., 1989) is a self-report scale developed to measure the quality of sleep. The scale consists of 19 items rated by the person and 5 rated by the bed/room mate that are not included in the total score. Items are grouped into 7 composite items rated on a 0–3 scale that yield a total score of 0–21, with higher scores denoting more sleep problems. A score >5 indicates the presence of a sleep disorder. The instrument proved to have good psychometric properties and to be able to distinguish good from bad sleepers.

The Epworth Sleepiness Scale (ESS, Johns, 1991) was developed to measure diurnal sleepiness. It consists of 8 items rated from 0 to 3. The total score ranges from 0 to 24, with higher scores denoting a higher likelihood of sleepiness. ESS scores significantly distinguished normal subjects from patients in various diagnostic groups including obstructive sleep apnea syndrome, narcolepsy and idiopathic hypersomnia. ESS scores were significantly correlated with sleep latency measured during the multiple sleep latency test and during overnight polysomnography. In patients with obstructive sleep apnea syndrome, ESS scores were significantly correlated with the respiratory disturbance index and the minimum SaO_2 recorded overnight. ESS scores of patients who simply snored did not differ from controls.

The SF-12 (Ware et al., 1995) is a validated and widely used health-related quality of life measure. It consists of 12 items that are aggregated into two summary measures of physical health (PCS) and mental health (MCS), expressed as T-scores (mean=50, SD=10), where higher scores denote a better health-related quality of life.

The Paffenbarger Physical Activity Questionnaire (Paffenbarger et al., 1993) is an eight-item validated instrument that is used to measure self-reported weekly duration and intensity of physical activity.

In order to measure adherence to the HLI program, an ad hoc questionnaire was developed for the present study that includes four questions: one explores the extent to which the patient was able to follow the instructions received in the previous week (1=never, 2=part of the week, 3=almost the entire week, 4=every day), the second rates the quality of the material received (1=good, 2=sufficient, 3=insufficient, 4=poor, 5=very poor), the third rates the ability of the physician to explain the program (1=good, 2=sufficient, 3=insufficient) and the fourth assesses motivation to adhere to the program (1=yes, 2=no).

2.2. Healthy lifestyle intervention

Patients were randomized to receiving a healthy lifestyle intervention (HLI) and drug treatment, or usual care and drug treatment. Patients assigned to HLI were assessed at the end of the intervention and were followed up for 12 months after the conclusion of the intervention; controls were assessed and followed up at the same times.

The HLI is a comprehensive, standardized, and integrated manualized program that helps patients to develop and maintain a healthy and active lifestyle. The HLI provides support and reinforcement to patients in order to achieve the desired results. The HLI was developed after reviewing the literature on the topic, with the aim to develop a program suitable for Italian patients with recurrent depression (major depressive or bipolar disorder) in the remission phase. In designing the study and the manual, the authors were particularly influenced by the lessons of E. Frank, M. Marcus, D. Kupfer, A. Germain, and M. Hall, who designed a similar study and intervention aimed at reducing medical risk in individuals with bipolar disorder (Frank et al., 2015). The HLI manual was developed after a review of the literature on the topic and of the manual that the authors above had designed for patients with bipolar disorder. All information was then adapted to both unipolar and bipolar patients and to Italian culture and habits. The manual did not undergo psychometric testing. Indeed, the present study was intended to test the usefulness, acceptability and feasibility of both the intervention and the manual itself.

The HLI aims to: 1) minimize the medical risk factors and promote quality of life; 2) improve the quality of sleep, 3) promote physical activity and, when necessary, weight loss; 4) promote the reduction/cessation of smoking. For smoking patients, the smoking sessions were optional.

The HLI consisted of individual sessions lasting 45–60 min held by psychiatrists and dieticians (only for sessions 7–8) and focused on the following topics (see Table 2):

1. the importance of life balance
2. psychoeducation on mood disorders
3. hygiene of social rhythms
4. sleep hygiene
5. the energy balance
6. physical exercise
7. nutritional education
8. eating and drinking: a matter of behavior
9. losing weight with physical exercise
10. addressing 'relapses' into bad eating habits and sedentary life
11. (optional) the harm caused by smoking
12. (optional) ways to quit smoking

Session 1 is an introduction to the experimental intervention and emphasizes the importance of balance between what a person has to do and wants to do in daily life and of a regular daily routine.

Session 2 provides an overview on the prevalence, symptoms, causes, course and treatments of mood disorders, including the pharmacological, psychological and other interventions (for instance herbal supplements, such as St. John's wort).

The sessions on social rhythms (session 3) and sleep hygiene (session 4) are based on the close connection between sleep disorders and mood disorders and on the importance of insomnia in the onset of an acute episode (depressive or manic) and its prognosis. The Sleep hygiene module includes elements of psychoeducation and monitoring of the sleep-wake cycle. Patients are helped to learn the connection between the breaking of the sleep routine and the onset of mood symptoms. Patients are prompted to increase the regularity of their daily routine, especially for what pertains the time in going to bed and waking up. Also, patients are helped to recognize and change all the habits that may interfere with a healthy sleep hygiene. The importance of dietary habits and physical activity as important zeitgebers for circadian system, essential in maintaining a regular sleep-wake cycle and social rhythms, is stressed out throughout the entire module. Changes related to the sleep-wake cycle, or to the social rhythms, are monitored via the SRM (Social Rhythm Metric) (Monk et al., 1990).

The sessions on energy balance and physical activity (sessions 5 and 6) aim at providing education about the importance of physical exercise and at promoting the inclusion of regular physical activity in the daily activities. The key elements include the identification of targets for the weekly energy expenditure, the development of a program for regular physical activity, aiming at a gradual increase in physical activity over time. The participation in the program is facilitated using motivational and behavioral techniques and progressive targets to achieve moderate levels of physical exercise are suggested. Pedometers are also used and the Paffenberger Activity Questionnaire (Paffenbarger et al., 1993) is completed to monitor and facilitate progress.

The sessions on eating, drinking, losing weight with physical exercise and preventing 'relapses' into bad eating habits and sedentary life (sessions 7–10) are focused on the importance of proper nutrition and regular meals. Sessions are based on the Dietary Guidelines for Americans 2005 (US Department of Health & Human Services and US Department of Agriculture, 2005), adapted to Italian eating habits. The key elements include appropriate choice of food, education about dietary guidelines, about the nutritional values of foods and beverages, and about fat, sugars, and cholesterol. This module promotes healthy food choices gradually. A modest loss of weight, between 5% and 10%, is aimed for overweight or obese patients, to be achieved through a weight loss

Table 2
Summary description of Healthy Lifestyle Intervention sessions.

	Topics	Therapeutic targets
1. The importance of life balance	• Measuring the balance between what the person is willing to do and what has to do in daily life	• Identifying potential imbalances in daily activities
2. Psychoeducation on mood disorders	• Education on prevalence, symptoms, causes, course and treatments of mood disorders	• Increase awareness and knowledge of mood disorders • Self-monitoring of depressive and manic symptoms
3. Hygiene of social rhythms	• Education on sleep-wake cycle disturbance in relation to mood disorders	• Self-monitoring of the sleep-wake cycle and social rhythms
4. Sleep hygiene	• Relationship between disruption of rhythms and the onset and maintenance of symptoms • Emphasis on regularity and education about healthy habits to favor sleep • Effect of nicotine, alcohol and other substances on sleep and on the social rhythms • Eating habits and physical activity: essential elements for achieving good social rhythms and a healthy sleep-wake cycle. • Relapse prevention	• Achieving and maintaining a regular sleep-wake cycle and regular social rhythms through the gradual regularization of sleep • Self-monitoring of nutrition and physical activity as important social zeitgebers
5. The energy balance	• Measuring energy expenditure • Education on the role of a healthy physical and mental energy balance in preventing mood episode	• Identify ways to measure and improve mental and physical energy expenditure
6. Physical exercise	• Education on the importance of physical activity and strategies to find the time to integrate exercise in the weekly routine • Education on how to be more active and how to exercise safely • Identification of ways to take an interest and get pleasure from physical activity • Strategies to stay motivated	• Identify the number of minutes to devote to exercise, to increase gradually over four weeks • Including in daily activities physical exercise of moderate intensity for 30 min 3 to 5 times a week
7. Nutritional education	• Education about healthy eating habits	• Improve/maintain self-monitoring of food ingestion
8. eating and drinking: a matter of behavior	• Making healthy food choices • Eat fewer calories and less fat • Alcohol and weight management • Maintaining a healthy diet and weight loss	• If indicated: reduction of 500 calories per day in a progressive way
9. Losing weight with physical exercise	• How to lose weight (if necessary) • Exercise and weight loss • Maintaining a weight loss	• If indicated: achieve a modest weight loss (5–10% of initial weight)
10. Addressing 'relapses' into bad eating habits and sedentary life	• Education about the difference between lapses and relapses and ways to cope with them	• Develop strategies to see a relapse as an occasion for a change as opposed to an occasion to give up
11. (Optional) the harm caused by smoking and ways to quit smoking	• Review of the effects of smoking on health	• Self-monitoring of the ways and stimuli to smoke
12. (Optional) stop smoking.	• Education about the interactions between nicotine and the drugs used to treat depressive disorder • Strategies to control the urge to smoke • Identify the relationships between smoking, sleep patterns and social rhythms, and eating habits • Education about the signs of recovery of smoking • Education about available resources for people who quit smoking	• Identify the benefits for smoking cessation • Plan to quit smoking: identification of a day and the best ways to stop smoking • Identify and amplify the strengths to be used to resist the urge to smoke

is 0,5–1 kg per week (i.e., decreasing the calories by 500–1000 per day). This approach proved to be effective in patients with severe mental illness (Alvarex-Jimenez et al., 2006; Mauri et al., 2006). Each participant is helped to develop a meal plan in line with individual preferences, and to achieve and maintain a healthy body weight. A daily food diary and the Fat & Fiber Behavior Questionnaire (FFB, Kristal et al., 1990) is used to monitor progress and difficulties in adhering to a healthy choice of food for a healthy eating program.

The two optional sessions (sessions 11 and 12) on smoking cessation are primarily based on the cognitive behavioral approach of the American Cancer Society's FreshStart Program (Shiffman and Cline, 1990). The FreshStart Program has been shown to achieve a 22% success rate (Lando et al., 1990). The program is focused on the acquisition of skills to address the discontinuation of smoking habits and includes psychoeducation on nicotine addiction and the delivery of strategies to promote and sustain smoking termination.

All sessions were conducted via face-to-face psychoeducational meetings with a psychiatrist and/or (for sessions 7 and 8) a dietician. The manual instructions concerning exercise, diet, and sleep hygiene were reviewed together with the patients. Reading materials and handouts were provided for homework. Each subject was asked to attend 10 sessions (12 if they elected to participate in the smoking cessation module). Each new session started with a summary of the previous sessions, which allowed a better personalization of the intervention, through the possibility to allocate more time to boost those issues that were particularly important for the individual patient. The assessment visits coincided with the HLI sessions for patients assigned to the experimental group. The intervention phase lasted 10 weeks for patients who attended sessions 1 to 10 and 12 weeks for those who also attended the 2 optional sessions on smoking cessation.

2.3. Statistical analyses

The sample size was defined assuming a 25% difference in relapse rate between the experimental group and the control group. The sample size required to reject the null hypothesis of equality of the relapse rate between the HLI group and the control group with a power of 90% and a Type-I probability of error of 0.05 is 124 (62×2). Anticipating a drop-out of 20% of patients, the

recruitment of 160 patients is sufficient to test the hypothesis of the study, using the χ^2-test. Continuous variables were summarized as means ± SD and categorical variables as percentage frequencies. The primary outcome (percentage of relapses) was compared between the study groups using the χ^2-test. The risk of relapse was estimated using Kaplan-Meier analysis and was compared between the study groups using log-rank test. Secondary outcomes, including changes in vital parameters and scale scores from baseline to three months, were examined in HLI patients and controls who completed the three-month assessment. Specifically, changes were analysed within each group, using the paired-samples *t*-test, and between groups using the independent-samples *t*-test or Wilcoxon W test when appropriate. In addition, linear mixed effects models with restricted maximum likelihood estimation were used to compare between groups the course of depressive symptoms, functioning and BMI over three months. These models take advantage of the information collected at each visit to estimate the linear trend over time of the outcome of interest. All analyses were carried out using SPSS, version 20.

3. Results

3.1. Study participants

The flow chart of study participants is provided in Fig. 1. Of the 160 eligible patients, 81 were randomized to HLI and 79 to the control group. In the HLI group, 64 received the allocated intervention and 48 completed the intervention. Five patients participated in the optional module of smoking cessation. In the control group, 54 initiated and 43 completed the intervention.

Patients had a mean age of 49 years and were 80% female, 73% had at least a high school educational level, 55% were married or living with partner, 9.3% were unemployed (Table 3). 105 had bipolar disorder and 55 recurrent unipolar depression. Twenty-two percent of participants were smokers, and 75.8% had tried a diet at least once. The mean BMI was 31 kg/m^2(SD 5.5), mean diastolic blood pressure was 77.4 mmHg (SD 10.7), and mean systolic blood pressure 119.3 mmHg (SD 11.3). Concerning physical activity, at baseline 39.6% reported to exercise on a regular basis, and 20.8% occasionally.

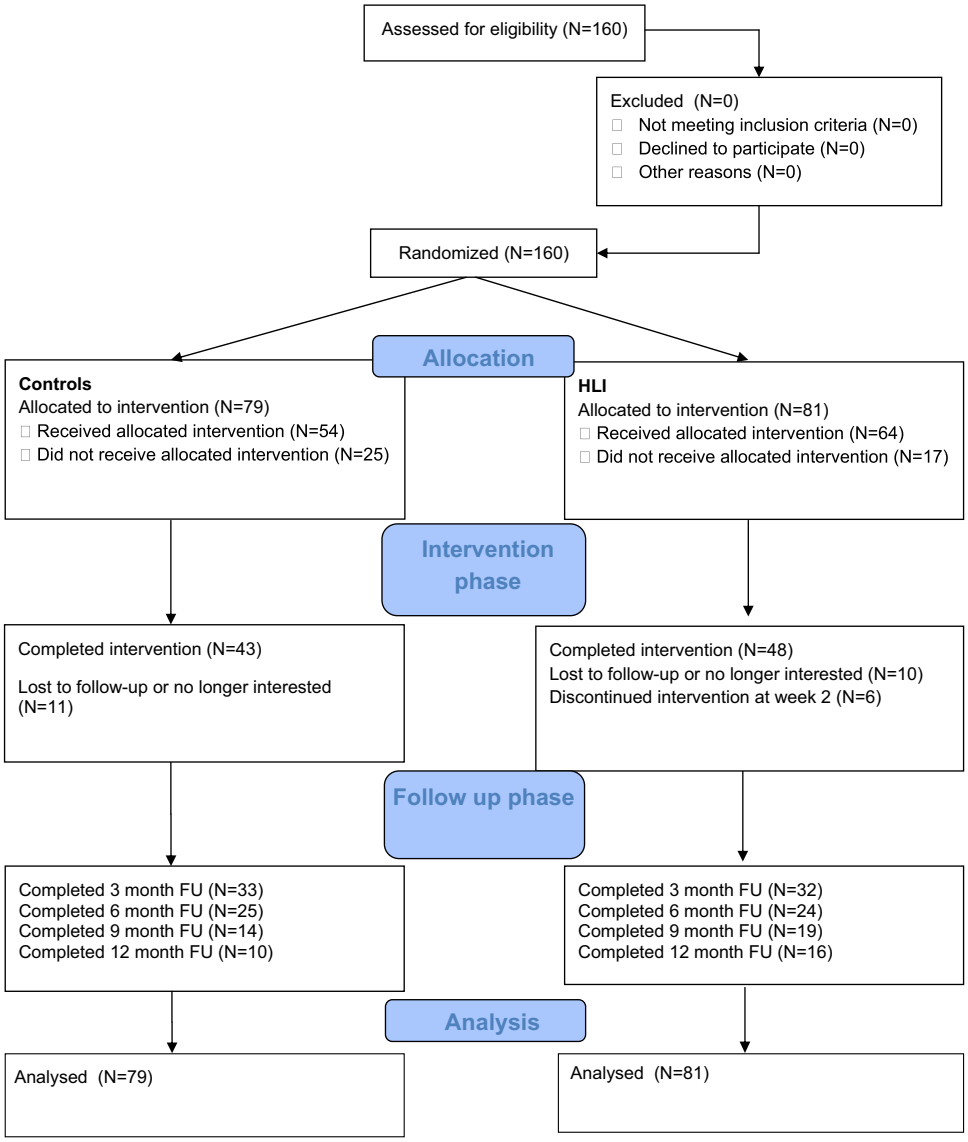


Fig. 1. Flow diagram of the study.

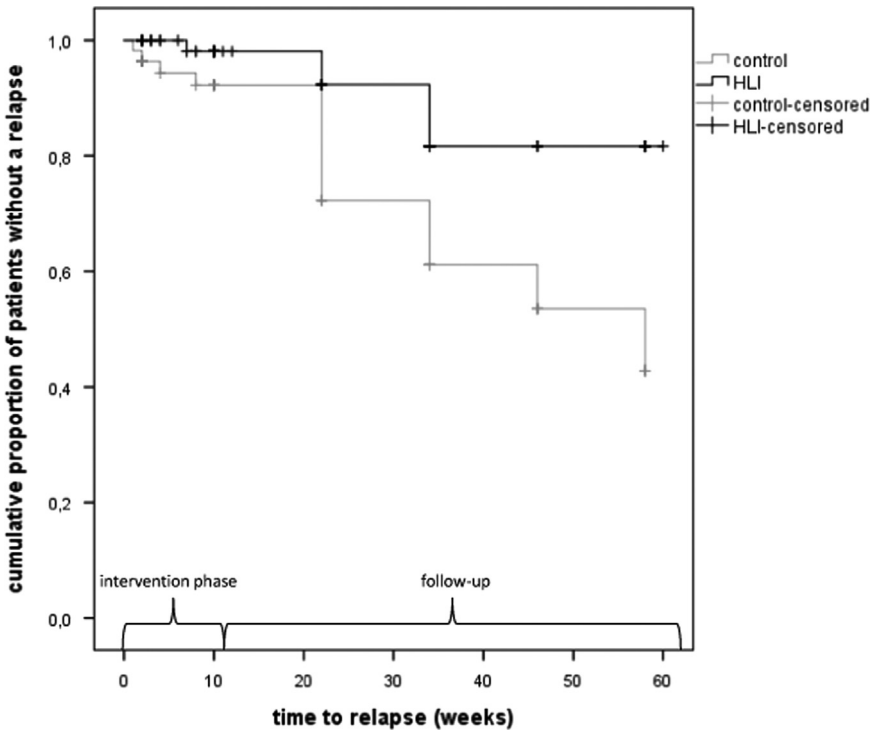


Fig. 2. Kaplan-Meier estimates of time to relapse in the study groups.

3.2. Outcomes

3.2.1. Primary outcome

During the intervention phase, 1 relapse occurred in the HLI group, and 4 in the control group. Over the 12 month follow-up, relapses were 5 in the HLI group and 16 in control group. Using an intent-to-treat approach, the overall percentage of relapses was 6/81 (7.4%) in the HLI group vs. 20/79 (25.3%) in the control group ($\chi^2=9.4$,df=1, p=0.002). Using a per-protocol approach, i.e. considering only those who received at least one visit after the beginning of the intervention, relapses were 6/64 (9.4%) in the HLI group and 20/54 (37.0%) in the control group ($\chi^2=13.0$, df=1, $p<0.001$). In a Kaplan-Meier analysis, patients in the HLI group were significantly less likely to experience a relapse compared with the patients assigned to the control group (log-rank test=8.77, p=0.003, Fig. 2).

Among patients with bipolar disorders, the percentage of relapses was significantly lower in those assigned to the HLI group than in those assigned to the control group (9.4% vs. 30.8%, $\chi^2=7.5$, df=1, p=0.006) and among patients with unipolar depression, the percentage of relapses was lower in the HLI group, but not significantly (3.6% vs. 14.8%, $\chi^2=2.1$, df=1, p=0.147). Kaplan-Meier analysis confirmed that patients with bipolar disorder assigned to the HLI group had a significantly lower risk of relapse compared to those assigned to the control group (log-rank test=6.03, p=0.014), while no difference in risk was found in patients with unipolar depression (log-rank test=2.05, p=0.152).

3.2.2. Other outcomes at the end of the intervention phase

Changes in scale scores and vital parameters at the end of the intervention phase are reported in Tables 4 and 5. All HLI patients and 82% of control patients were rated as mildly to highly improved on the CGI-I, with a significantly higher benefit (p=0.0116) in HLI patients (Table 4).

Concerning within-group comparisons, a significant reduction in PHQ-9, ESS scores and BMI and weight was found in HLI patients, while for all the other scales and vital parameters changes were not significant either for HLI patients or controls.

Between-group comparisons indicated that the reduction of BMI, weight and waist circumference was higher in HLI vs. controls. Quality of life improved in the HLI group, compared with the control group, but not significantly, both in the mental health and in the physical health component. The improvement in depressive symptomatology and functioning (PHQ-9 and WSAS) in the HLI group did not differ significantly from that observed in the control group. Sleepiness was reduced in the HLI group, compared with controls, but not significantly. No differences were found on quality of sleep. Fig. 3a–c shows the mean PHQ-9 and WSAS scores and BMI values during the intervention phase in the two study groups.

3.2.3. Time trend of outcomes during the intervention phase

Linear mixed models were carried out to compare the trend of depressive symptomatology, functioning and BMI between the two study groups over 10 weeks of the intervention phase. Because only 5 patients attended the smoking sessions at weeks 11 and 12, we did not include in the analyses these time points.

The estimated improvement in depressive symptomatology (PHQ-9) in the HLI group was about 1.7 points and did not differ significantly from that in the control group, about 0.4 points (F=1.67, df=92.4, p=0.20). Still, it is to be noted that the level of depressive symptoms was low at baseline in both groups. Functioning (WSAS) improved about one point in the HLI group (from 8.3 to 7.5) and remained stable in controls (F=0.32, df=102.7, p=0.57).

The estimated change in BMI was $+0.61$ kg/m^2 in the control group and -0.26 kg/m^2 in the HLI group, with significant differences between groups (F=6.04, df=30.77, p=0.02).

3.2.4. HLI program adherence

Of the 64 patients who initiated the HLI, 48 completed the program, 10 (15%) discontinued it and 6 were terminated for

Table 3
Demographic characteristics of study participants.

	HLI	Control	p
Age[a] (mean ± SD)	49.45 ± 12.65	48.80 ± 11.53	0.74
Gender			
F	66 (81.5%)	62 (78.5%)	0.64
M	15 (18.5%)	17 (21.5%)	
Educational level[a]			
Primary OR secondary school	19 (38.8%)	18 (36%)	0.53
High school	17 (34.7%)	24 (48%)	
University degree	11 (22.4%)	7 (14%)	
Post graduated	2 (4.1%)	1 (2%)	
Work[a]			
Artisan	1 (2.1%)	0	0.58
House wife	7 (14.6%)	5 (10.2%)	
Dealer	3 (6.3%)	3 (6.2%)	
Entrepreneur	1 (2.1%)	4 (8.2%)	
Freelance	1 (2.1%)	1 (2%)	
Student	2 (4.2%)	1 (2%)	
Retired	11 (22.9%)	8 (16.3%)	
Unemployed-searching for job	2 (4.2%)	7 (14.3%)	
Trainee	0	1 (2%)	
Temporary worker	4 (8.3%)	1 (2%)	
Permanent worker	16 (33.3%)	18 (36.7%)	
Currently smoking[a]			
No	41 (83.7%)	36 (72%)	0.16
Yes	8 (16.3%)	14 (28%)	
Ever on a diet?[a]			
No	13 (26.5%)	11 (22%)	0.60
Yes	36 (73.5%)	39 (78%)	
Marital status[a]			
Single	12 (25%)	15 (30%)	0.71
Living with partner	1 (2.1%)	1 (2%)	
Divorced	4 (8.3%)	4 (8%)	
Separated	1 (2.1%)	4 (8%)	
Married	27(56.3%)	25 (50%)	
Widowed	3 (6.2%)	1 (2%)	
Living arrangement[a]			
With partner	1 (3.6%)	1 (3.3%)	1.00
Alone	4 (14.3%)	5 (16.7%)	
Extended family	2 (7.1%)	2 (6.7%)	
Own family	21 (75%)	22 (73.3%)	
Annual income (Euro)[a]			
< 9.000	4 (9.1%)	10 (23.3%)	0.15
≥ 9.000 – 15.000	8 (18.2%)	11 (25.6%)	
> 15.000–20.000	1 (2.3%)	6 (13.9%)	
> 20.000–25.000	7 (15.9%)	3 (7%)	
> 25.000–30.000	5 (11.4%)	3 (7%)	
> 30.000–35.000	7 (15.9%)	5 (11.6%)	
> 35.000–45.000	5 (11.3%)	3 (7%)	
> 45.000–60.000	4 (9.1%)	1 (2.3%)	
> 60.000	3 (6.8%)	1 (2.3%)	

χ^2 test was used to compare categorical variables between groups; t-test was used to compare the mean age between groups.

[a] Missing data: 3 for age; 61 for educational level, currently smoking and ever on a diet; 63 for work; 62 for marital status; 102 for living arrangement; 73 for annual income.

medical reasons. The majority (50/64, 78.1%) attended at least 5 HLI sessions. More than 50% reported that they had followed the prescriptions daily or for most of the week. More than 89% of patients rated the quality of the material received good, and more that 97% rated the ability of the physician to explain the program good and virtually all (> 95%) felt motivated throughout the program.

4. Discussion

Many studies have evaluated the efficacy of exercise to reduce depressive symptoms, and most of them have reported a positive benefit associated with exercise involvement (Craft and Perna, 2004). Research also suggests that the benefits of exercise are long lasting (DiLorenzo et al., 1999).

Hence, we expected that a healthy lifestyle intervention, primarily based on physical activity, sleep hygiene, and healthy diet would have significant and clinically important mental health benefits for patients with depression.

Our results indicate that a combined and standardized healthy lifestyle intervention is efficacious in preventing relapses in patients with recurrent depression in remission and confers a risk reduction during the intervention phase and the 12-month follow-up period. This finding is consistent with evidence from the literature indicating that lifestyle modifications reduce stress, wards off anxiety and feelings of depression, boosts self-esteem and improve sleep (Sarris et al., 2014). Besides improving the mood disorder, a healthy lifestyle offers other health benefits, such as lowering blood pressure, protecting against heart disease and cancer.

Among patients with unipolar depression, the percentage of relapses was clearly lower in the HLI group (3.6% vs. 14.8%), but did not achieve statistical significance, whereas among patients with bipolar disorders, the percentage of relapses was lower in those assigned to the HLI group than in those assigned to the control group (9.4% vs. 30.8%) and the difference was statistically significant. Hence, our study confirms that a lifestyle intervention holds high likelihood to reduce new episodes of depression in patients with mood disorders in general and in patients with bipolar disorder in particular. We believe that exercise, sleep hygiene and promotion of a healthy diet should be considered as a key component of maintenance treatment for patients with depressive episodes. However, this kind of intervention is still underused in current practice.

Indeed many depressed patients receive predominantly pharmacologic therapy, with fewer receiving adjunct cognitive or behavioral interventions (Olfson et al., 2002). As a result, a number of patients are not appropriately educated regarding non-pharmacologic strategies for managing and preventing the symptoms of their depression.

Concerning secondary outcomes we found a significant reduction in depressive symptoms (PHQ-9) in the HLI group. Patients' self-report was consistent with the interviewer-rated CGI improvement. This finding indicates that even when patients are in the maintenance phase and have low levels of depressive symptoms there is room to achieve a full recovery. Our result has clinical implications because residual depressive symptoms are well-known predictors of relapse and poor psychosocial and functional outcomes during continuation and maintenance treatment (Prien and Kupfer, 1986; Mendlewicz, 2008).

Weight loss proved to be higher in the HLI compared with control group, even though not substantive in absolute terms and lower than expected, given the average BMI of patients at study entry. Our results are consistent with Frank et al. (2015), who reported a modest BMI reduction in patients with bipolar disorder in remission after a 6-month intervention including a healthy lifestyle program. Moreover, they are consistent with a meta-analysis (Fabricatore et al., 2002) showing that lifestyle modification is superior to control and non-dieting interventions for reducing symptoms of depression, and marginally better than dietary counseling and exercise-alone programs. However, our findings also suggest that more efforts should be devoted to help patients reduce (or to have them monitor) calories intake and increase physical activity in order to improve the efficacy of the intervention.

Table 4
Within- and between-group differences in scale scores from baseline to the last intervention visit.

	HLI			Control			
	First visit	Change	Within group p value	First visit	Change	Within Group p value	Between group p value
Functioning and quality of life							
SF-12							
PCS	45.87 ± 10.22	1.43 ± 7.60	0.43	46.52 ± 8.97	−3.40 ± 10.73	0.24	0.14
MCS	42.13 ± 13.01	3.75 ± 14.18	0.28	44.69 ± 11.79	−0.36 ± 10.42	0.89	0.36
WSAS	8.88 ± 8.05	−1.89 ± 8.16	0.17	7.62 ± 7.41	0.12 ± 8.94	0.94	0.33
Symptomatology							
PHQ-9	6.56 ± 4.82	−2.42 ± 4.06	0.001	6.08 ± 4.95	−0.76 ± 6.26	0.17	0.29
CGI-S	2.31 ± 1.28	−0.32 ± 1.18	0.09	2.38 ± 1.10	−0.19 ± 1.08	0.32	0.67
CGI-I							
(% Improvement at v10)		100%			82.0%		0.01
Sleep							
ESS	6.98 ± 4.18	−1.53 ± 3.83	0.037	4.93 ± 4.91	0.13 ± 3.81	0.85	0.10
PSQI total	6.97 ± 3.22	0.64 ± 3.29	0.54	7.42 ± 3.92	−1.60 ± 2.07	0.16	0.19

Paired *t* test or Wilcoxon signed rank sum test were used to analyse differences within groups, while *t*-test or Wilcoxon-Mann Whitney test were used to analysed changes between groups. χ^2test was used only to compare the percentage of patients who exhibited mild to high improvement (CGI-I) between groups.
Abbreviations: SF-12 Short form survey, PCS physical component, MCS mental component, WSAS Work and Social Adjustment Scale, PHQ−9 Patient Health Questionannaire, CGI-S Clinical Global Impressions, Severity, CGI-I Clinical Global Impressions, Improvement; ESS Epworth Sleepiness Scale, PSQI Pittsburgh Sleep Quality Index.

As to sleep, some improvement was observed for sleepiness (ESS) in the HLI group, but not for the quality of sleep.

Our results should be interpreted in light of some important limitations. First, our ability to engage and retain patients in the study was limited by the fact that they were recruited during the maintenance phase and that their main gain to participate in the study was the opportunity to participate at no cost in the HLI. Hence, there was not much interest to remain in the study after the 3-month intervention program, just to provide follow up information.

Second, a longer follow-up period would have been necessary to establish the long term effect of HLI.

Third, relapse may have occurred at the end of the intervention phase; however due to the drop out numbers during the follow-up phase in both treatment arms, our relapse rates are underestimated.

Fourth, the study is underpowered to detect the differential benefit of the program in the two diagnostic groups and our conclusions suggesting a significant reduction of recurrences only in patients with bipolar disorder warrant further confirmation.

Fifth, the PSQI questionnaire has many missing data because information on sleep quality was difficult to retrieve, therefore our results are based on a limited number of patients.

While keeping in mind these limitations, our results indicate that maintenance treatment of clinical depression can be improved by the addition of a healthy lifestyle programs.

Healthy lifestyle interventions hold promise to improve depression outcomes, and the findings of this study suggest that health care providers could promote the use of similar programs as a key tool to prevent new episodes of depression in patients with mood disorders.

Disclosure

Prof. Fagiolini has designed and coordinated the study and written the paper.

Drs. Goracci, Casolaro, Campinoti, Bolognesi and Valdagno have recruited patients, conducted the clinical study and the assessments and contributed to the interpretation of the results.

Dr. Rucci has conducted the data analysis and written the paper.

Dr. Forgione has developed the database, written the manual for the healthy lifestyle intervention and participated in data analysis.

Dr. Carretta has conducted the data analysis and participated in paper writing.

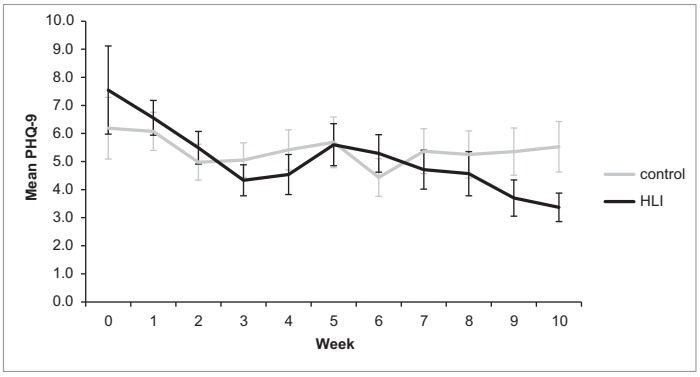
All the authors have approved the final version of the manuscript.

Table 5
Within and between group differences from baseline to the last intervention visit in vital parameters.

	HLI			Control			
	First visit	Change	Within group p value	First visit	Change	Within group p-value	Between group p-value
BMI (kg/m^2)	31.59 ± 5.72	−0.49 ± 0.89	0.001	30.39 ± 5.26	0.46 ± 2.01	0.004	≪ 0.001
Weight (Kg)	85.97 ± 17.21	−1.34 ± 2.36	0.001	83.14 ± 17.97	1.10 ± 6.07	0.01	≪ 0.001
Diastolic Blood pressure (mmHg)	77.50 ± 10.40	0.21 ± 10.50	0.48	77.19 ± 11.06	0.36 ± 10.83	0.88	0.82
Heart rate (bpm)	73.72 ± 7.43	−0.40 ± 6.44	0.63	74.66 ± 8.42	1.82 ± 7.77	0.14	0.13
Hips circumference (cm)	114.24 ± 12.16	−0.83 ± 4.90	0.28	109.41 ± 13.53	−0.25 ± 4.85	0.33	0.10
Systolic Blood pressure (mmHg)	120.18 ± 11.12	1.79 ± 14.85	0.51	118.33 ± 11.50	0.69 ± 11.90	0.49	0.27
Waist circumference (cm)	102.38 ± 13.91	−1.94 ± 6.33	0.01	97.92 ± 13.87	0.97 ± 4.72	0.11	0.002

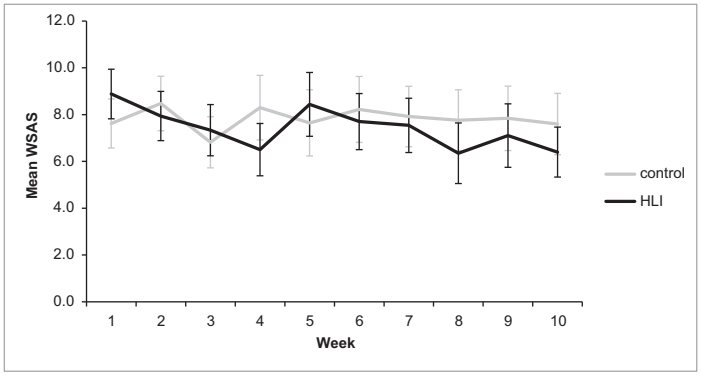
Wilcoxon signed rank sum test was used to analyse within groups differences, while Wilcoxon-Mann Whitney test was used to analysed changes between groups.

a



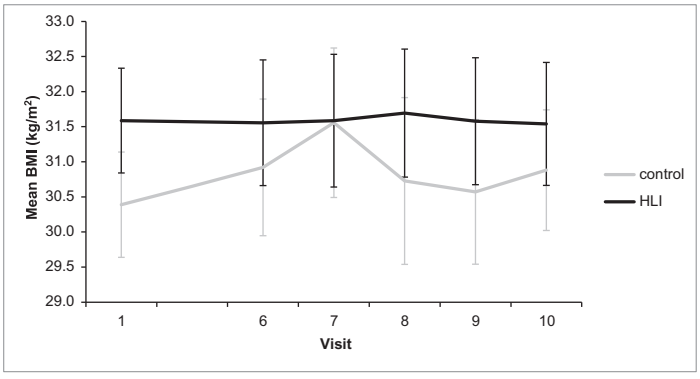
Week	0	1	2	3	4	5	6	7	8	9	10
Control	16	27	43	40	36	35	37	38	36	34	40
HLI	11	53	53	48	41	45	45	45	44	40	38

b



Week	1	2	3	4	5	6	7	8	9	10
Control	50	36	33	30	31	32	36	33	31	37
HLI	58	46	42	38	39	40	39	40	39	38

c



Week	1		6	7	8	9	10
Control	49		30	34	33	30	40
HLI	59		39	37	39	40	44

Fig. 3. a. Empirical mean ± 1SE PHQ-9 total score from the baseline to the 10th week in HLI patients and controls. b. Empirical mean ± 1SE WSAS total score from the 1st to the 10th week in HLI patients and controls. c. Empirical mean ± 1SE BMI from the 1st to the 10th week in HLI patients and controls.

Acknowledgements

The authors gratefully acknowledge IDEA Foundation for funding the study. This organization had no role in defining in study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

References

Almeida, O.P., Pfaff, J.J., 2005. Sleep complaints among older general practice patients: association with depression. Br. J. Gen. Pract. 55, 864–866.

Alvarex-Jimenez, M., Gonzalez-Blanch, C., Vazquez-Barquero, J.L., Perez-Iglesias, R., Martinez-Garcia, O., Perez-Pardal, T., Ramirez-Bonilla, M.L., Crespo-Facorro, B., 2006. Attenuation of *anti*psychotic-induced weight gain with early behavioral intervention in drug-naïve first-episode psychosis patients: A randomized controlled trial. J. Clin. Psychiatry 67, 1253–1260.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American Psychiatric Association, Washington, DC.

Bjornebekk, A., Mathé, A.A., Brene, S., 2006. Running has differential effects on NPY, opiates, and cell proliferation in an animal model of depression and controls. Neuropsychopharmacol 31, 256–264.

Bjørnebekk, A., Mathé, A.A., Brené, S., 2005. The antidepressant effect of running is associated with increased hippocampal cell proliferation. Int. J. Neuropsychopharmacol. 8, 357–368.

Bonifazi, M., Suman, A.L., Cambiaggi, C., Felici, A., Grasso, G., Lodi, L., Mencarelli, M., Muscettola, M., Carli, G., 2006. Changes in salivary cortisol and corticosteroid receptor-alpha mRNA expression following a 3-week multidisciplinary treatment program in patients with fibromyalgia. Psychoneuroendocrinology 31, 1076–1086.

Brene, S., Bjornebekk, A., Aberg, E., Mathé, A.A., Olson, L., Werme, M., 2007. Running is rewarding and *anti*depressive. Physiol. Behav. 92, 136–140.

Breslau, N., Roth, T., Rosenthal, L., Andreski, P., 1996. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol. Psychiatry 39, 411–418.

Buchheit, M., Gindre, C., 2006. Cardiac parasympathetic regulation: respective associations with cardiorespiratory fitness and training load. Am. J. Physiol. Heart Circ. Physiol. 291, H451–H458.

Buysse, D.J., Reynolds 3rd, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 28 (2), 193–213.

Chang, P.P., Ford, D.E., Mead, L.A., Cooper-Patrick, L., Klag, M.J., 1997. Insomnia in young men and subsequent depression: the Johns Hopkins precursors study. Am. J. Epidemiol. 146, 105–114.

Chen, M.J., Russo-Neustadt, A.A., 2007. Running exercise- and antidepressant-induced increases in growth and survival-associated signaling molecules are IGF-dependent. Growth Factors 25, 118–131.

Cole, M.G., Dendukuri, N., 2003. Risk factors for depression among elderly community subjects: a systematic review and meta- analysis. Am. J. Psychiatry 160, 1147–1156.

Craft, L.L., Perna, F.M., 2004. The benefits of exercise for the clinically depressed. Prim. Care Companion J. Clin. Psychiatry 6, 104–111.

Dishman, R.K., Berthoud, H.R., Booth, F.W., Cotman, C.W., Edgerton, V.R., Fleshner, M.R., Gandevia, S.C., Gomez-Pinilla, F., Greenwood, B.N., Hillman, C.H., Kramer, A.F., Levin, B.E., Moran, T.H., Russo-Neustadt, A.A., Salamone, J.D., Van Hoomissen, J.D., Wade, C.E., York, D.A., Zigmond, M.J., 2006. Neurobiology of exercise. Obesity 14, 345–356.

DiLorenzo, T.M., Bargman, E.P., Stucky-Ropp, R., Brassington, G.S., Frensch, P.A., LaFontaine, T., 1999. Long-term effects of aerobic exercise on psychological outcomes. Prev. Med. 28, 75–85.

Dryman, A., Eaton, W.W., 1991. Affective symptoms associated with the onset of major depression in the community: findings from the US national institute of mental health Epidemiologic catchment area program. Acta Psychiatr. Scand. 84, 1–5.

Dunn, A.L., Trivedi, M.H., Kampert, J.B., Clark, C.G., Chambliss, H.O., 2005. Exercise treatment for depression: efficacy and dose response. Am. J. Prev. Med. 28, 1–8.

Dunn, A.L., Trivedi, M.H., O'Neal, H.A., 2001. Physical activity dose–response effects on outcomes of depression and anxiety. Med. Sci. Sports Exerc. 33, S587–S597.

Dunn, A.L., 1996. Getting started—a review of physical activity adoption studies. Br. J. Sports Med. 30, 193–199.

Fabricatore, A.N., Wadden, T.A., Higginbotham, A.J., Faulconbridge, L.F., Nguyen, A. M., Heymsfield, S.B., Faith, M.S., 2002. Intentional weight loss and changes in symptoms of depression: a systematic review and meta-analysis. Int. J. Obes. 35, 1363–1376.

Fagiolini., A., Frank, E., Houck, P.R., Mallinger, A.G., Swartz, H.A., Buysse, D.J., Ombao, H., Kupfer, D.J., 2002. J. Clin. Psychiatry 63 (6), 528–533.

Fagiolini, A., Kupfer, D.J., Houck, P.R., Novick, D.M., Frank, E., 2003. Obesity as a correlate of outcome in patients with bipolar I disorder. Am J. Psychiatry 160, 112–117.

First, M.B., Spitzer, R.L., Gibbon M., Williams, J.B.W., 2002. State Psychiatric Institute, New York.

Ford, D.E., Kamerow, D.B., 1989. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA 262, 1479–1484.

Frank, E., Wallace, M.L., Hall, M., Hasler, B., Levenson, J.C., Janney, C.A., Soreca, I., Fleming, M.C., Buttenfield, J., Ritchey, F.C., Kupfer, D.J., 2015. An integrated risk reduction intervention can reduce body mass index in individuals being treated for bipolar I disorder: results from a randomized trial. Bipolar Disord. 17 (4), 424–437.

Galper, D.I., Trivedi, M.H., Barlow, C.E., Dunn, A.L., Kampert, J.B., 2006. Inverse association between physical inactivity and mental health in men and women. Med. Sci. in Sports Exerc. 38, 173–178.

Garcia-Toro, M., Roca, M., Monzón, S., Vives, M., Oliván, B., Vicens, E., Salva, J., Gili, M., 2012. Hygienic-dietary recommendations for major depression treatment: study protocol of a randomized controlled trial. BMC Psychiatry 12, 201. http://dx.doi.org/10.1186/1471-244X-12-201.

Garza, A.A., Ha, T.G., Garcia, C., Chen, M.J., Russo-Neustadt, A.A., 2004. Exercise, antidepressant treatment, and BDNF mRNA expression in the aging brain. Pharmacol., Biochem. Behav. 77, 209–220.

Goodwin, F.K., Jamison, K.R., 2007. Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression. Oxford University Press, New York.

Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, Rockville, MD.

Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14 (6), 540–545.

Keller, M.B., Lavori, P.W., Friedman, B., Nielsen, E., Endicott, J., McDonald-Scott, P., Andreasen, N.C., 1987. The longitudinal interval follow-up evaluation. A comprehensive method for assessing outcome in prospective longitudinal studies. Arch. Gen. Psychiatry 44 (6), 540–548.

Kristal, A.R., Shattuck, A.L., Henry, H.J., 1990. Patterns of dietary behavior associated with selecting diets low in fat: reliability and validity of a behavioral approach to dietary assessment. J. Am. Diet. Assoc. 90, 214–220.

Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16 (9), 606–613.

Lando, H.A., McGovern, P.G., Barrios, F.X., Etringer, B.D., 1990. Comparative evaluation of American Cancer Society and American Lung Association smoking cessation clinics. Am. J. Public. Health 80, 554–559.

Livingston, G., Blizard, B., Mann, A., 1993. Does sleep disturbance predict depression in elderly people? a study in inner London. Br. J. Gen. Pract. 43, 445–448.

Mallon, L., Broman, J.E., Hetta, J., 2000. Relationship between insomnia, depression, and mortality: a 12-year follow-up of older adults in the community. Int. Psychogeriatr. 12, 295–306.

Martinsen, E.W., Medhus, A., Sandvik, L., 1985. Effects of aerobic exercise on depression: a controlled study. Br. Med. J. (Clin. Res. Ed.) 291, 109.

Martinsen, E.W., Strand, J., Paulsson, G., et al., 1989. Physical fitness levels in patients with anxiety and depressive disorders. Int. J. Sports Med. 10, 58–61.

Mauri, M., Castrogiovanni, S., Simoncini, M., Iovieno, N., Miniati, M., Rossi, A., Dell'Agnello, G., Fagiolini, A., Donda, P., Cassano, G.B., 2006. Effects of An educational intervention on weight gain in patients treated with *anti*psychotics. J. Clin. Psychopharmacol. 26, 462–466.

Mendlewicz, J., 2008. Towards achieving remission in the treatment of depression. Dialog. Clin. Neurosci. 10, 371–375.

Monk, T.H., Flaherty, J.F., Frank, E., Hoskinson, K., Kupfer, D.J., 1990. The social rhythm metric. An instrument to quantify the daily rhythms of life. J. Nerv. Ment. Dis. 178, 120–126.

Morawetz, D., 2003. Insomnia and depression: which comes first? Sleep. Res. Online 5, 77–81.

Morgan, W.P., 1968. Selected physiological and psychomotor correlates of depression in psychiatric patients. Res. Q 30, 1037–1043.

Mundt, J.C., Marks, I.M., Shear, M.K., Greist, J.H., 2002. The work and social adjustment scale: a simple measure of impairment in functioning. Br. J. Psychiatry 180, 461–464.

Ohayon, M.M., Roth, T., 2003. Place of chronic insomnia in the course of depressive and anxiety disorders. J. Psychiatr. Res. 37, 9–15.

Olfson, M., Marcus, S.C., Druss, B., Elinson, L., Tanielian, T., Pincus, H.A., 2002. National trends in the outpatient treatment of depression. JAMA 287, 203–209.

Otto, M.W., Church, T.S., Craft, L.L., Greer, T.L., Smits, J.A., Trivedi, M.H., 2007. Exercise for mood and anxiety disorders. J. Clin. Psychiatry 68, 669–676.

Paffenbarger Jr, R.S., Blair, S.N., Lee, I.M., Hyde, R.T., 1993. Measurement of physical activity to assess health effects in free-living populations. Med. Sci. Sports Exerc. 25 (1), 60–70.

Perlis, M.L., Giles, D.E., Buysse, D.J., Tu, X., Kupfer, D.J., 1997. Self-reperted sleep disturbante as a prodromal symptom in recurrent depression. J. Affect. Disord. 42, 209–212.

Perlis, M.L., Smith, L.J., Lyness, J.M., Matteson, S.R., Pigeon, W.R., Jungquist, C.R., Tu, X., 2006. Insomnia as a risk factor for onset of depression in the elderly. Behav. Sleep. Med. 4, 104–113.

Prien, R.F., Kupfer, D.J., 1986. Continuation drug therapy for major depressive episodes: how long should it be maintained? Am. J. Psychiatry 143, 18–23.

Rethorst, C.D., Trivedi, M.H., 2013. Evidence-based recommendations for the prescription of exercise for major depressive disorder. J. Psychiatr. Pract. 19, 204–212.

Riemann, D., Voderholzer, U., 2003. Primary insomnia: a risk factor to develop depression? J. Affect. Disord. 76, 255–259.

Roberts, R.E., Shema, S.J., Kaplan, G.A., Strawbridge, W.J., 2000. Sleep complaints and depression in an aging cohort: a prospective perspective. Am. J. Psychiatry 157, 81–88.

Rucci, P., Calugi, S., Miniati, M., Fagiolini, A., 2013. A review of self-report and interview-based instruments to assess mania and hypomania symptoms. J. Psychopathol. 19, 143–159.

Russo-Neustadt, A.A., Chen, M.J., 2005. Brain-derived neurotrophic factor and antidepressant activity. Curr. Pharm. Des. 11, 1495–1510.

Russo-Neustadt, A.A., Alejandre, H., Garcia, C., Ivy, A.S., Chen, M.J., 2004. Hippocampal brain-derived neurotrophic factor expression following treatment with reboxetine, citalopram, and physical exercise. Neuropsychopharmacology 29, 2189–2199.

Russo-Neustadt, A., Ha, T., Ramirez, R., Kesslak, J.P., 2001. Physical activity-antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model. Behav. Brain Res. 120, 87–95.

Russo-Neustadt, A.A., Beard, R.C., Huang, Y.M., Cotman, C.W., 2000. Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. Neuroscience 101, 305–312.

Russo-Neustadt, A., Beard, R.C., Cotman, C.W., 1999. Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. Neuropsychopharmacol 21, 679–682.
Saeed, S.A., Bruce, T.J., 1998. Seasonal affective disorders. Am. Fam. Physician 57, 1340–1346 1340-6, 1351-2.
Sarris, J., O'Neil, A., Coulson, C.E., Schweitzer, I., Berk, M., 2014. Lifestyle medicine for depression. BMC Psychiatry 14, 107. http://dx.doi.org/10.1186/1471-244X-14-107.
Scully, D., Kremer, J., Meade, M.M., Graham, R., Dudgeon, K., 1998. Physical exercise and psychological well being: a critical review. Br. J. Sports Med. 32, 111–120.
Shiffman, S., Cline, T.R., 1990. FreshStart Plus [Manual]. American Cancer Society, Pittsburgh, PA.
Trivedi, M.H., Greer, T.L., Church, T.S., Carmody, T.J., Grannemann, B.D., Galper, D.I., Dunn, A.L., Earnest, C.P., Sunderajan, P., Henley, S.S., Blair, S.N., 2011. Exercise as an augmentation treatment for nonremitted major depressive disorder: a randomized, parallel dose comparison. J. Clin. Psychiatry 72, 677–684.
Trivedi, M.H., Greer, T.L., Grannemann, B.D., Chambliss, H.O., Jordan, A.N., 2006. Exercise as an augmentation strategy for treatment of major depression. J. Psychiatr. Pract. 12, 205–213.
Tsuno, N., Besset, A., Ritchie, K., 2005. Sleep and depression. J. Clin. Psychiatry 66, 1254–1269.
U.S. Department of Health and Human Services, U.S. Department of Agriculture, 2005. Dietary Guidelines for Americans ⟨http://www.health.gov/dietaryguidelines⟩, Released January 12, 2.
Vollrath, M., Wicki, W., Angst, J., 1989. The Zurich study, VIII: insomnia: association with depression, anxiety, somatic syndromes, and course of insomnia. Eur. Arch. Psychiatry Neurol. Sci. 239, 113–124.
Ware, J.E., Kolinski, M., Keller, S.D., 1995. How to Score the SF-12 Physical and Mental Health Summaries: A User's Manual. The Health Institute, New England Medical Center, Boston, MA.
Weissman, M.M., Greenwald, S., Nino-Murcia, G., Dement, W.C., 1997. The morbidity of insomnia uncomplicated by psychiatric disorders. Gen. Hosp. Psychiatry 19, 245–250.
Wildes, J.E., Marcus, M.D., Fagiolini, A., 2006. Obesity in patients with bipolar disorder: a biopsychosocial-behavioral model. J. Clin. Psychiatry 67, 904–915.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435.