Late-life major depression is associated with individual suffering, increases in medical morbidity and mortality,1–3 healthcare service use and costs for society.4 Available antidepressant therapies currently provide unsatisfactory results, as no more than half of those treated reach remission after a single treatment course.5 Therefore, any viable and safe strategy that can improve the efficacy of antidepressant drugs will critically contribute to the management of late-life depression.6 It has been proposed that physical exercise could improve the effectiveness of pharmacological treatments in geriatric major depression.7,8 In fact, physical exercise can counteract key biological alterations linked with depression that are only partially modified by antidepressant drug therapy.9–10 It increases levels of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), and neurogenesis, leading to improvements in neurocognitive performance.11,12 Exercise also reduces pro-inflammatory cytokines and hypothalamic–pituitary–adrenal (HPA) axis activity.13,14 Moreover, physical exercise counteracts disability and social isolation,15 while improving psychological self-evaluation.13 So far, no study has tested such a hypothesis or examined whether the intensity of physical exercise influences its antidepressant effect, as it has been observed in younger adults.16 Our aim was therefore to investigate whether the combination of sertraline treatment with two types of physical exercise – higher-intensity, progressive aerobic exercise plus sertraline (S+PAE), lower-intensity, non-progressive exercise plus sertraline (S+NPE) and sertraline alone. The primary outcome was remission (a score of <10 on the Hamilton Rating Scale for Depression (HRSD)) of 18 or higher;17 and being 65 years or older.18 Exclusion criteria were other Axis I diagnoses, substance or alcohol misuse, cognitive impairment, defined as a Mini Mental State Examination (MMSE) score of less than 24,19 and the presence of severe or unstable physical illness that would prevent exercise (e.g. unstable angina, arrhythmias, severe osteoarthritis with functional limitations, uncontrolled diabetes, New York Heart Association class III heart failure, Parkinson’s disease, severe respiratory disease). The second visit was then programmed with the study cardiologist to assess aerobic capacity under electrocardiographic monitoring. Rest and peak maximum oxygen uptake (VO2max) was tested on a cycle ergometer (Corival, Lode Medical Technology, Groningen, The Netherlands) with breath-by-breath expired gas analysis (Oxycon

**Physical exercise for late-life major depression**


**Methods**

Interventions including physical exercise may help improve the outcomes of late-life major depression, but few studies are available.

**Aims**

To investigate whether augmenting sertraline therapy with physical exercise leads to better outcomes of late-life major depression.

**Method**

Primary care patients (>65 years) with major depression were randomised to 24 weeks of higher-intensity, progressive aerobic exercise plus sertraline (S+PAE), lower-intensity, non-progressive exercise plus sertraline (S+NPE) and sertraline alone. The primary outcome was remission (a score of <10 on the Hamilton Rating Scale for Depression (HRSD)).

**Results**

A total of 121 patients were included. At study end, 45% of participants in the sertraline group, 73% of those in the S+NPE group and 81% of those in the S+PAE group achieved remission (P = 0.001). A shorter time to remission was observed in the S+PAE group than in the sertraline-only group.

**Conclusions**

Physical exercise may be a safe and effective augmentation to antidepressant therapy in late-life major depression.

**Declaration of interest**

None.

**Copyright and usage**

© The Royal College of Psychiatrists 2015.
Pro Metabolimeter, CareFusion, Yorba Linda, California, USA). The test had a duration of 12 min: it began with a 3 min warm-up and was carried out with workload increments of 10 W/min for women and 15 W/min for men. The test was interrupted earlier than 12 min in the following conditions: muscular exhaustion, refusal of the patient to continue, respiratory quotient $> 1.03$, reaching the plateau of oxygen consumption. $^{20}$ The test was suspended and the participant excluded on appearance of signs of atrial fibrillation or other arrhythmias.

**Randomisation and masking**

Randomisation was performed after the cardiologist visit by computer with a randomised permutation blocks method (size of blocks 4), stratifying individuals according to study centre, severity of depression (Clinical Global Impression scale severity item mildly/moderately v. severely ill), $^{21}$ past treatments with antidepressant (yes v. no), age ($< 75$ years v. $\geq 75$ years) and gender. Each study centre coordinator was sent a personal email containing participants’ group assignments and was allowed to share this information only with the study instructors, while keeping the clinical assessor unaware of participant allocation. Also, participants were asked not to disclose to the clinical assessors the type of intervention they were receiving.

**Interventions**

Participants were randomly assigned to receive sertraline only ($n = 42$), sertraline plus supervised group non-progressive exercise ($n = 37$) or sertraline plus supervised group progressive aerobic exercise ($n = 42$).

Sertraline

Patients in the sertraline-only condition were prescribed the drug by the centre psychiatrists, with a slow titration scheme to reach the standard dosage of 50 mg within 2 weeks. The choice of sertraline was based on its safety and efficacy in elderly patients and on its low potential for pharmacological interactions. $^{22}$ The prescribing dosage was decided on according to clinical response and the presence of side-effects, in accordance with routine clinical practice. For insomnia, daily use of a hypnotic (zolpidem up to 10 mg/day or lorazepam up to 2 mg/day) was allowed during the first 4 weeks of treatment and discouraged later. At each visit participants were asked to bring their medications to verify their adherence to the prescription scheme. Episodes of non-adherence, defined as not taking the prescribed dosage for at least 3 consecutive days, were recorded.

Sertraline plus non-progressive exercise

Participants in the sertraline plus non-progressive exercise (S+NPE) arm received sertraline as in the sertraline-only group. In addition they were prescribed attendance at three supervised group exercise sessions per week (60 min duration) for 24 weeks in groups of three to six participants. These sessions were designed to improve participants’ strength, balance, respiration and motor coordination, and comprised both mat work and instrumental exercises (see Appendix). Sessions were conducted using heart-rate monitors with on-screen visualisation (Polar Team, Polar Electro, Woodbury, New York, USA). Participants in this group were assigned to exercise at heart rate ranges designed not to exceed 70% of their peak rate. Participants who exceeded their established peak heart rate were asked by the instructor to reduce the intensity of the exercise until their heart rate recovered.

Sertraline plus progressive aerobic exercise

Participants assigned to sertraline plus progressive aerobic exercise (S+PAE) received sertraline as in the sertraline-only study arm. The schedule of exercise sessions overlapped with those of S+NPE group (three 60 min sessions per week for 24 weeks, in groups of three to six participants). The exercises were mainly based on the use of exercise bicycles, aimed at improving cardiopulmonary condition. $^{23,24}$ Each session began with a 10 min warm-up breathing exercise, followed by cycling at an intensity that would maintain the heart rate within the assigned training range (60% of peak heart rate). Exercise intensity was monitored by the instructor using heart-rate meters as in the S+NPE arm. The training scheme was programmed to increase over the weeks, adapting to possible increases in peak heart rate, and to include brief sessions of interval training. All exercise sessions concluded with 5–10 min of cool-down cycling (see Appendix).

**Assessments**

Psychiatric diagnoses were assigned by study psychiatrists after administration of the Mini International Neuropsychiatric Interview (MINI). $^{25}$ Assessments took place at baseline and after 4 weeks, 8 weeks, 12 weeks and 24 weeks (within no more than 3 days of the scheduled visit): they included a physical examination, general and psychiatric history, administration of the MMSE, the Cumulative Illness Rating Scale (CIRS), $^{26}$ MINI, HRSD, Clinical Global Impression (CGI) scale and the International Physical Activity Questionnaire (IPAQ). $^{27}$ Assessors were already extensively trained in the use of these instruments; however, four meetings held to improve interrater reliability on a set of five illustrated cases. Participants who refused to undertake any further assessment with the study personnel were considered to have left the study.

**Outcomes**

The primary outcome of this study was the rate and time to remission from depression over the 24-week period, with remission defined as an HRSD score of 10 or below; this scale rates symptoms and signs of depression occurring during the week preceding its administration. Secondary outcomes were changes in severity of depression (continuous HRSD scores), global improvement of depression (CGI) and changes in aerobic capacity.

**Statistical analysis**

A post hoc power analysis showed that a sample size of 40 patients per intervention arm (120 participants) would give an 85% power to detect a 30% difference in remission rates (35% v. 65%, $P < 0.05$) and a 92% power to detect a standardised mean difference of 0.34 in HRSD scores ($P < 0.05$), similar to the effect yielded by a recent meta-analysis. $^{6}$ We aimed at assessing the superiority of each combined intervention (S+NPE and S+PAE) compared with antidepressant drug treatment for remission rates, time to remission and other secondary outcomes. To estimate differences in the time to achieve remission we used a survival analysis with Kaplan–Meier estimates of the survival function. A Cox regression analysis was then performed to test whether results held after adjustment for demographic and clinical confounders. To analyse the patterns of change in depression scores over time we performed multilevel hierarchical growth curve analysis using repeated HRSD scores as the dependent variable (baseline, 4 weeks, 8 weeks, 12 weeks and 24 weeks), nested within individual and study centre. The linear, quadratic and cubic terms of time were...
also tested as fixed parameters, along with the interaction terms with group.\textsuperscript{28} Estimation of the parameters was done using the maximum likelihood method and heterogeneous autoregressive covariance structure. Analyses were carried out in the intention-to-treat population, using the last observation carried forward (LOCF) method to impute missing data. All analyses were performed using SPSS version 15.0 on Windows 7.

Results

Eligible participants were recruited from January 2011 to June 2012. A total of 121 patients entered the study and were randomised to the three treatments: 42 in the sertraline group, 37 in the S+NPE group and 42 in the S+PAE group (Fig. 1). Most participants were recruited in the Bologna East centre (sertraline \(n=18\), S+NPE \(n=17\), S+PAE \(n=18\)), smaller numbers were drawn from Bologna West (sertraline \(n=11\), S+NPE \(n=10\), S+PAE \(n=9\)), Parma (sertraline \(n=10\), S+NPE \(n=4\), S+PAE \(n=9\)) and Modena–Correggio (sertraline \(n=3\), S+NPE \(n=6\), S+PAE \(n=6\)). Participants’ demographic and clinical characteristics are reported in Table 1. Their mean age was 75 years (s.d. = 6); the majority were women, most were not married and had elementary or lower educational level. The most frequent physical comorbidities were hypertension (64%), musculoskeletal problems (61%), metabolic–endocrinological disorders (40%) and conditions relating to eye, ear, nose and throat (39%). The median HRS\(D\) score for the whole sample was 18 (interquartile range (IQR) 18–22), indicating mild to moderate severity of depressive symptoms; most participants had already been treated with antidepressant drugs at some point in their lives – more than 80% with a selective serotonin reuptake inhibitor (SSRI).

Attrition, safety and adherence

A few people withdrew from the study; six from the sertraline only arm, five from the S+NPE arm and four from the S+PAE arm (14%, 14% and 10% respectively; \(\chi^2=0.50\), d.f. = 2, \(P=0.78\)). Reasons for withdrawing were unwillingness to remain in the study (\(n=10\), new medical problems (\(n=4\)) and the need for higher level of care for depression (\(n=1\)). Common mild side-effects attributable to the medication included nausea, diarrhoea and insomnia and were rare. Two people left the study because of incidents correlated with physical exercise (one in the S+NPE group and one in the S+PAE group), one for ankle distortion and the other for worsening of musculoskeletal pain. The majority of participants attended assessment visits, with no significant between-group difference (sertraline 79%, S+NPE 78%, S+PAE 81%; \(\chi^2=0.10\), d.f. = 2, \(P=0.95\)). All participants received 50 mg of sertraline at entry. By the study end 43% of those in the sertraline-only group had their dosage increased by the study psychiatrists, as opposed to 22% in the S+NPE group and 17% in the S+PAE group (\(\chi^2=8.121\), d.f. = 2, \(P=0.02\); pairwise comparisons \(P<0.05\)). The rate of non-adherence to sertraline treatment tended to be higher in those in the drug-only arm (26%) than in the combined interventions (S+PAE 7%, S+NPE 16%, \(\chi^2=5.53\), d.f. = 2, \(P=0.06\)). Attendance at exercise sessions was high (70% for 72 total sessions) and similar in the two exercise groups (S+PAE median 54 sessions, IQR 44–64; S+NPE median 51 sessions, IQR 38–58; Mann–Whitney \(z=2.167\), \(P=0.14\)), with a tendency to decrease over the follow-up period.

Remission of depression

Remission rates were higher in the S+PAE and S+NPE groups than in the sertraline-only group: at week 4, rates were 36%, 40% and 7% respectively (\(P=0.001\)). At week 8, rates were 60%, 49% and 40% (\(P=0.22\)) and at week 12 they were 83%, 54% and 45% (\(P=0.001\)). By the study end, remission was achieved by 45% of participants in the sertraline group, 73% of those in the S+NPE group and 81% of those in the S+PAE group (\(P=0.001\)). Figure 2 reports survival curves for the three intervention groups; in Kaplan–Meier analyses time to remission was significantly different between groups (log rank \(\chi^2=12.6\), d.f. = 2, \(P=0.002\)): this was driven by a shorter time to remission

\begin{figure}
\centering
\includegraphics[width=\textwidth]{study_profile.png}
\caption{Study profile.}
\end{figure}
in the S+PAE group (9.3 weeks, 95% CI 7.4–11.2) than in the sertraline group (14.8 weeks, 95% CI 12.2–17.4), whereas the time to remission was intermediate for the S+NPE group (12.0 weeks, 95% CI 9.2–14.8). Compared with participants in the drug-only group, those in the S+PAE group had a twofold hazard ratio for an earlier remission; this value survived after adjusting for various study contextual and clinical factors (Table 2). Furthermore, the hazard ratio for the S+NPE group also became statistically significant with a similar value (1.91) when the same factors were taken into account.

Changes in depressive symptoms

There were greater decreases in HRSD scores in the two exercise groups compared with the drug-only group (Table 3, Fig. 3). The overall time course of HRSD scores was best predicted by a third-order polynomial of time, and by the interactions of intervention group (S+NPE vs. sertraline and S+PAE vs. sertraline) with time (Table 4). This model’s fitness showed significant improvements over models including only the linear and quadratic terms of time (both 2LL decreases 445, d.f. = 3, \( P < 0.01 \)), whereas adjusting for the control variables did not lead to further improvement in the model fitness. There was no significant association between the baseline severity of depression and the rate of decrease over time (rho: \( P = 0.15 \)). Last, the percentage of participants rated as ‘very much improved’ or ‘much improved’ on the CGI (scores 1 and 2) at the study end was significantly higher in the S+PAE group (71%) and in the S+NPE group (60%) than in the sertraline-only group (43%; \( \chi^2 = 7.09, \text{d.f.} = 2, P = 0.03 \)).

Changes in aerobic capacity

Only 73 participants had their aerobic capacity assessed at both baseline and 24 weeks (25 in the S+NPE group, 34 in the S+PAE group and 14 in the sertraline group). Peak VO\(_2\) was on average stable among participants in the S+NPE group (\(-0.22\%; \text{IQR} = -14.5 \text{ to } -12.9\)), whereas those in the S+PAE group showed a median improvement of 4.7% (IQR = 10.3 to 16.8) and those in the sertraline-only group a decrease (\(-2.5\%; \text{IQR} = -18.6 \text{ to } -5.9\)). However, after adjusting for baseline peak aerobic capacity, intervention group did not predict aerobic capacity at 24 weeks (S+NPE group \( P = 0.22 \), S+PAE group \( P = 0.32 \)), whereas the number of sessions attended in both groups did (\( P = 0.03 \)).
A significantly higher proportion of sedentary older people with major depression achieved remission with sertraline plus a 24-week exercise programme compared with those treated with sertraline alone. Both the exercise protocols were associated with earlier and higher remission rates, which were evident after only 4 weeks of treatment. The beneficial effect of physical exercise was independent of the severity and chronicity of depression, of participants’ demographic characteristics and of physical comorbidities. Overall, a high degree of adherence to the interventions was observed in a frail population group that had not been sufficiently studied in this regard. These findings are particularly significant for clinical practice, since late-life depression is often associated with poor or slow responses to first-line pharmacotherapy, and with physical inactivity.

Other research
To our knowledge this study is the first to examine the efficacy of structured physical exercise interventions in the antidepressant treatment of older adults with major depression. Our findings are consistent with research suggesting that exercise could exert antidepressant properties in adults with subthreshold or fully fledged clinical depression. In older patients, most commonly with non-major depression, a few studies have shown that physical exercise (group- or home-based, strength training or mixed aerobic and strength training, mostly three times per week) was effective in reducing depressive symptoms, with small to moderate effects. Several factors may account for this difference:

Sertraline only
Sertraline plus non-progressive exercise
Sertraline plus progressive aerobic exercise

**Fig. 3** Unadjusted mean scores (with 95% confidence intervals) on the Hamilton Rating Scale for Depression (HRSD) over time.

### Discussion

### Table 2 Time to remission from depression: effect of sertraline v. integrated treatments

<table>
<thead>
<tr>
<th>Predictor</th>
<th>B (s.e.)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S+NPE</td>
<td>0.51 (0.27)</td>
<td>1.68</td>
<td>0.98–2.88</td>
</tr>
<tr>
<td>S+PAE</td>
<td>0.75 (0.26)</td>
<td>2.12**</td>
<td>1.27–3.54</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S+NPE</td>
<td>0.65 (0.29)</td>
<td>1.91*</td>
<td>1.08–3.39</td>
</tr>
<tr>
<td>S+PAE</td>
<td>0.72 (0.29)</td>
<td>2.04*</td>
<td>1.17–3.58</td>
</tr>
<tr>
<td>Centre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bologna East</td>
<td>−0.69 (0.30)</td>
<td>0.50*</td>
<td>0.28–0.89</td>
</tr>
<tr>
<td>Parma</td>
<td>0.44 (0.37)</td>
<td>1.56</td>
<td>0.76–3.21</td>
</tr>
<tr>
<td>Modena–Correggio</td>
<td>−0.38 (0.40)</td>
<td>0.68</td>
<td>0.31–1.50</td>
</tr>
</tbody>
</table>

Clinical factors
- Age
- Gender, male
- CIRS comorbidity score
- Baseline HRSD score
- Number of previous episodes of depression
- Prior treatment with antidepressants

Medication
- Dosage of sertraline
- Non-adherence to sertraline

CIRS, Cumulative Illness Rating Scale; HR, hazard ratio; HRSD, Hamilton Rating Scale for Depression; S+NPE, sertraline plus non-progressive exercise; S+PAE, sertraline plus progressive aerobic exercise.

*P<0.05; **P<0.01.

### Table 3 Severity of depression

<table>
<thead>
<tr>
<th>Assessment</th>
<th>HRSD total score: mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sertraline group (n=42)</td>
</tr>
<tr>
<td>Baseline</td>
<td>20.4 (3.4)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>15.8 (4.4)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>12.8 (5.0)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>11.7 (5.0)</td>
</tr>
<tr>
<td>24 weeks</td>
<td>11.7 (5.9)</td>
</tr>
</tbody>
</table>

HRSD, Hamilton Rating Scale for Depression; S+NPE, sertraline plus non-progressive exercise; S+PAE, sertraline plus progressive aerobic exercise.
these include the use of an antidepressant drug, social support due to exercising in groups, more intense exercise protocols and a longer duration of the interventions.\textsuperscript{13,16,32} More recently another study has found that a low-intensity, low-frequency tai chi plus meditation protocol in combination with escitalopram therapy was more effective than health education meetings plus escitalopram among older volunteers with depression from the community.\textsuperscript{33} In contrast, a recent large trial failed to demonstrate significant reductions of depressive symptoms associated with physical exercise (two sessions per week) among very old people living in care homes.\textsuperscript{34} This inconsistency might be due to differences in sample characteristics (participants were more physically and cognitively impaired and only half had clinical depression in the latter study), assessment instrument (Geriatric Depression Scale), a lower frequency, intensity and adherence to the physical exercise protocol and lower antidepressant use (30% of participants). Taken together, these findings suggest that physical exercise might not be managed along with an antidepressant,\textsuperscript{35} or at least be scheduled with sufficient frequency and/or intensity to exert significant antidepressant effects.\textsuperscript{13,16} In our study both protocols followed the recommendations set by guidelines for physical exercise in elderly people,\textsuperscript{13} but differed in that the S+PAE intervention was characterised by increasing energy expenditure, whereas the S+NPE group exercises were aimed at improving participants’ balance and strength. After adjusting for confounders, the outcomes of depression were similar in the two groups. Unlike others,\textsuperscript{35} we did not observe significant improvement in aerobic capacity in the exercise groups compared with the sertraline-only group, or between the two exercise groups. However, only a small number of participants (n=73) were assessed for aerobic capacity both at baseline and after 24 weeks, so the statistical power may have not been sufficient to detect the effect of exercise on the aerobic capacity. Further analyses and larger studies should clarify whether different types of physical activity might elicit specific mechanisms of antidepressant action in elderly patients,\textsuperscript{13,36} for example, among younger adults aerobic training but not strength exercise seems to be faster than is commonly observed for antidepressant therapy.\textsuperscript{36} We were unable to control for the effect of different instructors delivering exercise interventions, as each group was trained by the same instructor in all sessions. However, we held regular meetings for the monitoring of fidelity to protocols, and we did not observe any significant between-instructor difference in participants’ adherence. Despite randomisation, we observed imbalances in some baseline participant characteristics, perhaps a result of between-centre differences in patient flow. However, multivariate analyses showed that these factors did not affect the results significantly. All participants were recruited from referrals by primary care physicians. Therefore, our findings may not be generalisable to a broader population of elderly people with depression that might include individuals not seen or recognised by their physicians as depressed. Although the LOCF method is widely used, one of its limitations is the assumption that participants maintain their benefits even when they exit the study prematurely.

**Clinical implications**

Our findings provide the clinician with a rationale for adopting physical exercise as a potential tool in the management of late-life major depression; it is noteworthy that nearly three-quarters of the patients who received physical exercise as an add-on to sertraline therapy reached remission within the study period – well beyond those who received sertraline alone. Also, remission was faster than is commonly observed for antidepressant

### Study limitations

This study has some limitations that need to be taken into account. We did not include an active comparator, such as social support or health education group meetings, as an augmentation strategy to sertraline. Hence, we cannot rule out that part of the additional antidepressant efficacy provided by physical exercise was related to social support rather than to exercise itself.\textsuperscript{32} However, this choice was undertaken for several reasons: first, our aim was to assess the added benefit of exercise to SSRI therapy, since SSRIs are commonly used by primary care physicians and the low efficacy of these drugs leaves many patients with continuing symptoms.\textsuperscript{29} Second, physical exercise was already shown to be more effective than comparators such as social group programmes.\textsuperscript{7} Third, patients might have been less likely to engage in non-therapeutic activities with such a high frequency. Another limitation is that participants received relatively low dosages of sertraline, despite the fact that clinicians were free to increase the dose according to the clinical indication; however, the final dosages used in our study reflect usual clinical practice.\textsuperscript{38} We were unable to control for the effect of different instructors delivering exercise interventions, as each group was trained by the same instructor in all sessions. However, we held regular meetings for the monitoring of fidelity to protocols, and we did not observe any significant between-instructor difference in participants’ adherence. Despite randomisation, we observed imbalances in some baseline participant characteristics, perhaps a result of between-centre differences in patient flow. However, multivariate analyses showed that these factors did not affect the results significantly. All participants were recruited from referrals by primary care physicians. Therefore, our findings may not be generalisable to a broader population of elderly people with depression that might include individuals not seen or recognised by their physicians as depressed. Although the LOCF method is widely used, one of its limitations is the assumption that participants maintain their benefits even when they exit the study prematurely.

#### Table 4: Growth curve model for the changes in depressive symptoms with time

<table>
<thead>
<tr>
<th>Parameter</th>
<th>b</th>
<th>s.e.</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>19.87</td>
<td>0.45</td>
<td>18.99 to 20.75</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Time 1</td>
<td>−2.36</td>
<td>0.16</td>
<td>−2.67 to −2.06</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Time 2</td>
<td>0.17</td>
<td>0.02</td>
<td>0.13 to 0.20</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Time 3</td>
<td>−0.03</td>
<td>0.05</td>
<td>−0.04 to −0.03</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>S+NPE time</td>
<td>−0.22</td>
<td>0.45</td>
<td>−1.10 to 0.66</td>
<td>0.621</td>
</tr>
<tr>
<td>S+NPE time 2</td>
<td>−0.46</td>
<td>0.16</td>
<td>−0.77 to −0.16</td>
<td>0.003**</td>
</tr>
<tr>
<td>S+NPE time 3</td>
<td>0.06</td>
<td>0.02</td>
<td>0.01 to 0.09</td>
<td>0.007**</td>
</tr>
<tr>
<td>S+PAE time 2</td>
<td>−0.001</td>
<td>0.0005</td>
<td>−0.002 to −0.0003</td>
<td>0.010**</td>
</tr>
<tr>
<td>S+PAE time 3</td>
<td>−0.36</td>
<td>0.43</td>
<td>−1.21 to 0.49</td>
<td>0.399</td>
</tr>
<tr>
<td>S+PAE time 4</td>
<td>−0.44</td>
<td>0.15</td>
<td>−0.74 to −0.15</td>
<td>0.003**</td>
</tr>
<tr>
<td>S+PAE time 5</td>
<td>0.04</td>
<td>0.02</td>
<td>0.003 to 0.08</td>
<td>0.033*</td>
</tr>
<tr>
<td>S+PAE time 6</td>
<td>−0.01</td>
<td>0.05</td>
<td>−0.002 to 0.00043</td>
<td>0.060</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variance intercept</td>
<td>8.69</td>
<td>1.57</td>
<td>6.10 to 12.37</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Variance time</td>
<td>0.03</td>
<td>0.01</td>
<td>0.02 to 0.04</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>ARH rho</td>
<td>−0.20</td>
<td>0.14</td>
<td>−0.45 to 0.08</td>
<td>0.147</td>
</tr>
</tbody>
</table>

ARH, autoregressive heterogeneous covariance structure; S+NPE, sertraline plus non-progressive exercise; S+PAE, sertraline plus progressive aerobic exercise

a. Sertraline-only group is the reference category.

\*P < 0.05, **P < 0.01
treatment in elderly patients. Participants were representative of the sedentary patients with late-life major depression who are usually encountered in primary care: the vast majority had been treated with an antidepressant in the past for previous depressive episodes, but still experienced relevant – albeit mild to moderate – symptoms. All these factors have been linked with worse responses to antidepressant drugs, and might contribute to further disability, chronicity and worse outcomes. Although in this first report we did not examine potential mechanisms and predictors of response to physical exercise, further analyses might extend knowledge on these issues and help the translation of these results to clinical practice. We have documented that combining physical exercise of high or low intensity with antidepressants is more effective than antidepressant drug therapy alone in older adults with major depression who are sedentary. Clinicians may consider adding exercise to the regimen of older patients with depression, people who often fail to respond to antidepressant therapy.

Martino Belvederi Murri, MD; Section of Psychiatry, Department of Neuroscience, Ophthalmology, Genetics and Infant-Maternal Science, University of Genoa, Genoa, Italy, and Department of Psychobiology, Institute of Psychiatry, King’s College London, London, UK; Mario Amore, MD, PhD, Section of Psychiatry, Department of Neuroscience, Ophthalmology, Genetics and Infant-Maternal Science, University of Genoa, Genoa, Italy; Marco Mennetti, MD, PhD, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; Lucia Toni, MD, Cardiology Unit, Ramazzini Hospital, Bologna, Italy; Francesca Neveani, MD, PhD, Department of Geriatrics, Nuovo Ospedale Civile S. Agostino Estense, Modena and Reggio Emilia University, Modena; Matteo Cerri, MD, PhD, Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy; Marco B. L. Rocchi, Department of Biomedicine and Bioengineering, University of Bologna, Bologna, Italy; primary care physicians, Bologna; Enrico Tam, PhD, Department of Movement and Neurological Sciences, University of Verona; Angelia Buffa, MD, PhD, Unit of Internal Medicine, Geriatric and Nephrology, S. Orsola Malpighi Hospital, Bologna; Serena Ferrera, Psychologist, Consultation Liaison Psychiatry Service, Department of Mental Health, Bologna; Mirco Neri, Department of Geriatrics, Nuovo Ospedale Civile S. Agostino Estense, Modena and Reggio Emilia University, Modena; Martina A. S. Alexopoulos, MD, PhD, Department of Psychiatry, Weill Cornell Medical College, New York, USA; Stamatula Zaneddou, MD, Consultation Liaison Psychiatry Service, Department of Mental Health, Bologna, Italy; the Safety and Efficacy of Exercise for Depression in Seniors (SEEDS) Study Group.

Correspondence: Dr Martino Belvederi Murri, Clinica Psichiatrica, Ospedale S. Martino, Largo Rosanna Benzi, 10, 16132 Genova, Italy. Email: martino.belvederi@gmail.com

First received 28 Apr 2014, final revision 24 Oct 2014, accepted 24 Nov 2014

Funding

This research was supported by the Emilia Romagna Region University Programme (PHR) 2010-2012 grant, Area 2 for Clinical Governance. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Acknowledgements

Members of the Safety and Efficacy of Exercise for Depression in Seniors (SEEDS) study group include the following. Bologna centres: Francesco Ripa di Meana, MD, Maria L. Montali, MD, Aderville Cabassi, MD, PhD, Mattia Masotti, MD, PhD, and Maria Lidia Gerra, MD. Bologna centres: Ferdinando Tripi, MD, Massimo Mannina, MD, Di Diodoro, MD, Giovanni Neri, MD, Carlo Spezia, MD, Monica Magagnoli, MD, Claudia Luciano, MD, Federica Casini, PsyD, Giuliano Emrni, MD, Piero Casarin, MD, Pier Vittorio Bardazzi, MD, Alessandro Piras, MD, PhD, Giuliana Tola, Roberta Zio, Lorenzo De Iesi and Davide Comastri. Modena–Correggio centre: Ferdinando Trigi, MD, Massimo Mennini, MD, Massimo Hopski, MD, PhD, Sandro Zoboli, Gabriele Torcianti, Niccolò Comolli, MD, PhD, Federico Guido, MD, Silvia Ferrari, MD, PhD, Moreno Felliati, MD, Veronica Barbanti Silva, MD, Agnese Ceppellini, Elena Franzia, PsyD, Roberto Chesa, MD, and Anna Grazia Frigiani, MD. Parma centres: Cristina Montegnani, MD, PhD, Graziano Ceresini, MD, Arianna Mortali, MD, Adrielle Cassilesi, MD, PhD, Mattea Mascetti, MD, PhD, and Maria Lida Gerra, MD. Each session of the protocol consisted of:

10 min warm-up: walking, strengthening exercises, quiet calisthenics
2 repetitions of 10 min each: mat work: stretching, calisthenics, breathing exercises
2 repetitions of 5 min each: instrumental exercises (first with a ball, then with a stick)
2 repetitions of 5 min each: balance exercises (e.g. toe walking, heel to toe, single limb stance, staggered stance)
10 min cool down: walking, quiet calisthenics

Participants were invited to rest when their heart rate exceeded the threshold of 70% of peak heart rate, or whenever they felt exhausted.

Appendix

Protocol for the progressive aerobic exercise intervention

Each session of the protocol consisted of a 10 min warm-up: breathing exercises, slow cycling. This was followed by cycling at an intensity that would maintain the heart rate within the assigned target heart-rate range. Target heart rate was defined by percentage of the peak heart rate (PHR) as measured during the maximum oxygen uptake test. All exercise sessions concluded with 5–10 min of cool-down cycling.

Cycling sessions

First period (weeks 0–4): exercise bike, cycling at 60–70% of PHR, 30–40 min
Second period (weeks 5–8): treadmill exercise at 70–80% of PHR, 40–50 min
Third period (weeks 9–12): five interval training sessions of 5 min at 85% of PHR or 40 min of continuous treadmill at 70% of PHR
Fourth period (weeks 13–24): five interval training sessions of 6 min at 85% of PHR, or 40 min of continuous walking at 70% of PHR

References


10 Alexopoulos GS, Morimoto SS. The inflammation hypothesis in geriatric depression. Int J Geriatr Psychiatry 2011; 26: 1109–18.


Belvederi Murri et al


Physical exercise for late-life major depression

References
This article cites 0 articles, 0 of which you can access for free at:
http://bjp.rcpsych.org/content/early/2015/07/09/bjp.bp.114.150516#BIBL

Reprints/permissions
To obtain reprints or permission to reproduce material from this paper, please write to permissions@rcpsych.ac.uk

P<P
Published online 2015-07-23T00:05:15-07:00 in advance of the print journal.

You can respond to this article at
/letters/submit/bjprcpsych;bjp.bp.114.150516v1

Downloaded from
http://bjp.rcpsych.org/ on June 26, 2017
Published by The Royal College of Psychiatrists

Advance online articles have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.