Mental health literacy, folic acid and vitamin B₁₂, and physical activity for the prevention of depression in older adults: randomised controlled trial

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Background
Few randomised controlled trials (RCTs) have examined potential preventive agents in high-risk community populations.

Aims
To determine whether a mental health literacy intervention, the promotion of physical activity, or folic acid plus vitamin B₁₂ reduce depressive symptoms in community-dwelling older adults with elevated psychological distress.

Method
An RCT with a completely crossed 2×2×2 factorial design: (400 mcg/d folic acid + 100 mcg/d vitamin B₁₂ v. placebo) × (physical activity v. nutrition promotion control) × (mental health literacy v. pain information control). The initial target sample size was 2000; however, only 909 adults (60–74 years) met the study criteria. Interventions were delivered by mail with telephone calls. The main outcome was depressive symptoms on the Patient Health Questionnaire (PHQ–9) at 6 weeks, 6, 12 and 24 months. The Clinicaltrials.gov registration number is NCT00214682.

Results
The drop-out rate was low (13.5%) from randomisation to 24-month assessment. Neither folic acid + B₁₂ (F(3,856) = 0.83, P = 0.476) nor physical activity (F(3,856) = 1.65, P = 0.177) reduced depressive symptoms at any time point. At 6 weeks, depressive symptoms were lower for the mental health literacy intervention compared with its control condition (t(895) = 2.04, P = 0.042).

Conclusions
Mental health literacy had a transient effect on depressive symptoms. Other than this, none of the interventions significantly reduced symptoms relative to their comparator at 6 weeks or subsequently. Neither folic acid plus B₁₂ nor physical activity were effective in reducing depressive symptoms.

Declaration of interest
None.

Depression in later life is common with 3.6–4.8% of people over 60 years reporting 12-month major depression, and 8–37.4% report significant depressive symptoms.¹ ² Late-life depression may result in impaired cognitive, physical and social functioning, and predisposes to suicide.³ ⁴ It is estimated that by 2020 depressive disorders will be the second highest cause of disease burden,⁵ and the prevalence of depressive disorders is projected to double from its present level by 2050.⁶ In order to minimise the adverse impact of depression, effective, economical and accessible prevention strategies that are scalable to a community-wide level clearly need to be developed. Ideally, these should also build upon the community's preference for lifestyle and psychological interventions to maximise adherence.⁷ With the aim of developing effective preventive strategies, the first step is to identify interventions that reduce depressive symptoms in community-dwelling individuals. If successful, such interventions constitute the basis for larger indicated prevention trials.⁷ To date, however, the development and evaluation of such programmes has been minimal.

We identified three candidate interventions with potential utility for prevention in older people. Physical activity has been shown in some studies to be an effective treatment in mild to severe depression, with remission rates comparable with cognitive therapy or antidepressant medication.⁸ ⁹ Mediated physical activity programmes (e.g. interventions that are delivered entirely by the telephone, mail or the internet) may increase physical activity levels, suggesting a potential role for these non-intensive methods in large-scale preventive initiatives.¹⁰ Some programmes that improve mental health literacy have been found to reduce depression symptoms in a number of trials,¹¹ ¹² whereas others have found improved depression literacy but no change in depressive symptoms.¹³ There are indications from clinical and treatment studies that folate and vitamin B₁₂ may reduce or prevent depression.¹⁴ ¹⁵ Folic acid and vitamin B₁₂ supplementation may prevent depression by lowering homocysteine levels, which are elevated in individuals with depression and in some samples of older people.¹⁶ Low folate levels and vitamin B₁₂ have been found in community samples of adults with depression¹⁷ although the evidence is uncertain whether folate and vitamin B₁₂ offer effective treatment for depression.¹⁷ Supplementary folic acid and vitamin B₁₂ may reduce the long-term risk of onset of depression via reduction of vascular and other metabolic risk factors for late-life depression.¹⁸

The present study investigated the effectiveness of promoting physical activity, mental health literacy and combined folic acid and vitamin B₁₂ as preventive interventions for an older population with elevated psychological distress. A factorial 2 (folic acid + vitamin B₁₂, placebo) × 2 (physical activity promotion, control) design was chosen. This design had the advantage of testing multiple interventions in a single trial and incorporating appropriate control conditions for each intervention. Assuming either no interaction or
synergistic effects, factorial trials have the potential to evaluate multiple interventions against appropriate control conditions, effectively offering ‘three trials for the price of one’. Further, healthcare significance may be enhanced because each intervention is administered in the context of other interventions: there is evidence that consumers try multiple, simultaneous approaches to address both physical and mental health problems. Pain management materials served as the control for mental health literacy, nutrition information for physical activity promotion, whereas a placebo tablet was the control for folic acid + vitamin B_{12}. Because of our interest in developing an intervention that was genuinely scalable and applicable in community settings, the trial was entirely delivered by either telephone or mail with an emphasis on reducing the amount of person-to-person contact both at screening and in the delivery of the programme. As a consequence of this, we could not, and did not seek to formally diagnose individuals with clinical depression. Highly distressed individuals (Kessler Distress 10–Scale (K10) score of 30 or greater) were excluded as they were considered candidates for professional care rather than preventive management. However, the trial did not exclude participants with lower K10 scores who may have met clinical diagnostic criteria.

We hypothesised that mental health literacy, physical activity promotion, and/or folic acid (400 mcg/d) + vitamin B_{12} (100 mcg/d) would reduce depressive symptoms in a sample of community-dwelling individuals with subthreshold depression symptoms.

### Method

#### Study design

The study’s 2\times2 factorial design reflected the three interventions and their matched control interventions. Participants were randomised into one of the 8 intervention programmes arising from the combination of active or comparison conditions of each intervention type: placebo, physical activity promotion, mental health literacy; placebo, physical activity promotion, pain information; placebo, nutrition promotion, mental health literacy; placebo, nutrition promotion, pain information; folic acid + vitamin B_{12}, physical activity promotion, mental health literacy; folic acid + B_{12}, physical activity promotion, pain information; folic acid + B_{12}, nutrition promotion, mental health literacy; and folic acid + B_{12}, nutrition promotion, pain information. Outcomes were assessed at baseline, 6 weeks, 6, 12 and 24 months. Clinicaltrials.gov registration number is NCT00214682.

#### Participants

Participants were recruited from urban and rural sites by mail using address and age (60–74 years) information provided by the Australian Electoral Commission. These lists allowed representative population sampling as voting is compulsory in Australia.

Selected participants had elevated psychological distress as assessed by the K10 with scores 16 or greater (scores <16 indicate no or low levels of psychological distress);\(^{21}\) did not engage in physical activity at public health recommended levels as indicated by International Physical Activity Questionnaire (IPAQ) scores;\(^{22}\) did not take folic acid, vitamin B_{12} or vitamin B complex supplements; had no history of dementia, bipolar disorder or current suicide risk; had competent literacy skills; and did not have a medical condition that would contraindicate exercise or folic acid use. Individuals with high likelihood of a depressive disorder with K10 scores of 30 or greater\(^{23}\) were excluded. Those with low levels of red cell folate (<250 nmol/l) and vitamin B_{12} (<130 nmol/l), and abnormal thyroid-stimulating hormone levels (0.35–5.0 mu/l) were excluded as participation may have lead to potential adverse outcomes. Folate and vitamin B_{12} deficiency can lead to anaemia, fatigue, neurological degeneration, weight loss, red and painful tongue and heart palpitations.\(^{14}\) Thus it was unethical to recruit individuals with a medical need for supplementation.

Recruitment occurred between 22 October 2005 and 4 September 2006 with the 24-month intervention and data collection occurring from 4 January 2006 to 18 September 2008. Human research ethics committees at the Australian National University, Australian Capital Territory Health Department and the University of Sydney, Australia, approved the study. All participants provided written informed consent.

#### Interventions

Eligible participants were enrolled into an intervention programme that was delivered over 24 months in ten modules. All interventions involved five brief telephone tracking calls over the first 5 weeks and five more telephone calls at 4, 8, 13, 18 and 22 months, in order to motivate participants to read the material, facilitate their engagement with the project and material, and ensure that the material and related tasks have been understood – no supportive counselling was given. With the exception of the folic acid + vitamin B_{12} and placebo tablets, all interventions involved five modules of information delivered by mail in Weeks 1–5, followed by a further five modules sent out at 4, 8, 13, 18 and 22 months.

**Mental health literacy arm**

**Mental health literacy.** Modules 1–5 were contained in a depression literacy manual (www.beyondblue.org.au) including information regarding: prevalence and depressive symptoms; barriers to help-seeking such as stigma; prevention; the evidence for medical, psychological and alternative treatments; and resources for support and treatment of depression.\(^{25}\) The additional mental health literacy modules were booklets that addressed sleep, anxiety disorders and their treatment, structured problem-solving training, cognitive–behavioural strategies for depression and interpersonal therapy. These were developed by the Centre for Mental Health Research, Australian National University.

**Pain information.** Modules 1–5 involved an Arthritis Australia consumer guide for arthritis management\(^{26}\) and modules 6–10 were Arthritis Australia consumer guides on pain management, osteoporosis and falls prevention.

**Dietary supplementation arm**

**Folic acid + vitamin B_{12} tablets.** These were formulated as a daily oral dose of one tablet consisting of folic acid 400 mcg and vitamin B_{12} 100 mcg (Matchland Pty Ltd, t/a New Products Development –ABN57052101176, Brisbane, Australia). The folic acid dose of 400 mcg/d was selected as it has been shown to be associated with 90% of the maximal decrease in plasma homocysteine concentration for older adults.\(^{27}\) Following a safety review subsequent to a widely reported publication on the association between folate and colorectal adenomas,\(^{28}\) the protocol changed to two daily oral doses (folic acid 200 mcg and 50 mcg each) from July 2007 to minimise unmetabolised folic acid in the blood. Also as a consequence of the publicity given to a study reporting a possible link between folic acid and colon cancer,\(^{29}\) 26 participants withdrew from the study, and 72 participants stopped taking the
Questionnaire – Short Form (IPAQ–SF) was used as a self-report measure of physical activity. This survey lists 12 situations in which exposure to depression because of its brevity and community use. A modified version of the Level of Contact Report examined intimacy of contact with severe mental illness varies. There were differences between those that were enrolled into the intervention compared with individuals who failed to meet the criteria for selection. Reflecting inclusion criteria, at screening, participants who were randomised into the trial had higher psychiatric distress scores (K10 mean 20.43 ± 4.7). The Internet site random.org was used (conducted by J.G.W.) to randomly allocate a label ‘A’ or ‘B’ to the folic acid + vitamin B12, and placebo tablet bottles to ensure concealment of their content. Participants, interviewers, investigators and the survey administrators were masked to active intervention and folic acid placebo allocation. One participant was unmasked at 15 months because of impending medical treatment unrelated to the study. Participants were masked regarding the mental health literacy intervention and physical activity promotion as all of the intervention arms were delivered as a healthy ageing programme. Mixed-model repeated measures analysis of variance (MMRM) was used to evaluate hypotheses concerning differential change between each active intervention and its comparator. Within-person variation was modelled using an unstructured covariance matrix. Degrees of freedom were estimated using Satterthwaite’s approximation. Initial models included effects of each intervention arm and interaction between interventions. Final models only included tests for main effects as all interactions between the three interventions were not significant. As baseline data were complete, no imputation of baseline missing data was necessary. Mixed models yield an intention-to-treat analysis, using all available measurement points for each participant under the assumption that withdrawal data are missing at random. Version 15 of SPSS for Windows was used for all statistical analyses. Mixed-model repeated measures analysis of variance (MMRM) was used to evaluate hypotheses concerning differential change between each active intervention and its comparator. Within-person variation was modelled using an unstructured covariance matrix. Degrees of freedom were estimated using Satterthwaite’s approximation. Initial models included effects of each intervention arm and interaction between interventions. Final models only included tests for main effects as all interactions between the three interventions were not significant. As baseline data were complete, no imputation of baseline missing data was necessary. Mixed models yield an intention-to-treat analysis, using all available measurement points for each participant under the assumption that withdrawal data are missing at random. Version 15 of SPSS for Windows was used for all statistical analyses.

Results
Demographic characteristics and drop-out
There were differences between those that were enrolled into the intervention compared with individuals who failed to meet the criteria for selection. Reflecting inclusion criteria, at screening, participants who were randomised into the trial had higher psychological distress scores (K10 mean 20.43 vs. 14.42, F = 1023.46, F = 1023.46,
Fig. 1 Flow of participants through the trial.

Completers, participants completing the survey for that time point; non-completers, participants that did not complete the assessment at that time point but continued with the study and were assessed at the following time point; n/a, not applicable.
More were taking prescribed antidepressant medication (16.5% vs. 8.3%, \( \chi^2 = 71.82, P = 0.001 \)), as well as being younger (mean 65.94 years vs. 67.05 years; \( F = 49.35, P = 0.001 \)), and more likely to be female (\( \chi^2 = 24.00, P = 0.001 \)), separated/divorced or widowed (30.10% vs. 25.10%; \( \chi^2 = 11.98, P = 0.007 \)), as well as engaged in paid employment (34.3% vs. 32.4%; \( \chi^2 = 19.84, P = 0.001 \)) compared with those who did not meet the criteria. At screening, 739 individuals were excluded because of elevated K10 scores (>29 indicating high likelihood of a depressive disorder).23 Individuals with high K10 scores were significantly older (mean 67.30 years vs. 65.94 years, \( F = 35.71, P = 0.001 \)), reported fewer years of education (mean 11.78 vs. 13.85, \( F = 160.55, P = 0.001 \)), and by the nature of the study criteria had significantly higher K10 scores (mean 15.18 vs. 20.43, \( F = 2735.78, P = 0.001 \)), with more taking prescribed antidepressant medication (42.7% vs. 16.5%, \( \chi^2 = 126.77, P = 0.001 \)) than those randomised into the intervention trial.

There were no demographic differences at baseline among those randomised to different interventions (Table 1), except those who received folic acid + B12 reported more exposure to others with a mental illness than the placebo group (\( F(1,898) = 4.71, P = 0.030 \)). The drop-out rate was low, with only 123 (13.5%) participants withdrawing from the time of randomisation to the 24-month assessment. In total, 855 participants (94.0%) completed the 6-week interview, 825 (90.8%) did the 6-month interview, 797 (87.7%) the 12-month interview, and 752 (82.7%) completed the 24-month interview. There were no differences in the proportions of participants in each condition who completed the 24-month interview (folic acid + B12 vs. placebo: \( \chi^2(1) = 0.6, P = 0.42 \); physical activity vs. nutrition promotion: \( \chi^2(1) = 2.0, P = 0.16 \); mental health literacy vs. pain information: \( \chi^2(1) = 0.6, P = 0.44 \)).

### Folic acid + vitamin B12 and physical activity levels

Relative to placebo, the folic acid + B12 group experienced a significant folate increase (from 573 to 951 mmol/l; \( t(690) = 12.0, P < 0.001 \)) and B12 levels (from 305 to 475 mmol/l; \( t(681) = 14.5, P < 0.0001 \)) over the 24-month period. Homocysteine increased significantly less in the folic acid + B12 group (from 9.6 to 10.4) than in the placebo group (from 9.8 to 12.0; \( t(649) = -5.6, P < 0.001 \)). Physical activity increased over the first 6 weeks, but dropped to baseline levels at 6 months, significantly below baseline at 12 months (\( t(862) = -3.6, P < 0.001 \)) and below baseline at 24 months (\( t(834) = -1.7, P = 0.095 \)). Changes in activity over time between the physical activity and control groups were not significantly different at any time point (\( F(4,839) = 1.3, P = 0.26 \)).

### Depression scores

Overall, depression scores on the PHQ–9 dropped over the course of the trial (Table 2; \( F(3,856) = 43.93, P < 0.001 \)). Omnibus tests of time x intervention arm effects were not significant for folic acid + B12 (\( F(3,856) = 0.83, P = 0.476 \)), physical activity (\( F(3,856) = 1.65, P = 0.177 \)) or mental health literacy (\( F(3,856) = 1.87, P = 0.132 \)). However, mental health literacy was associated with significantly lower depression scores between baseline and 6 weeks compared with the control group (\( t(889) = -2.28, P = 0.023 \), effect size \( d = 0.12 \)). A trend of similar magnitude remained at 6 months but was not significant.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline participant characteristics for each treatment groupa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Folic acid + B12</strong></td>
<td><strong>Physical activity</strong></td>
</tr>
<tr>
<td><strong>Physical activity control</strong> (nutrition)</td>
<td><strong>Physical activity control</strong></td>
</tr>
<tr>
<td>(( n = 447 ))</td>
<td>(( n = 453 ))</td>
</tr>
<tr>
<td><strong>Age, years:</strong> mean (s.d.)</td>
<td>65.92 (4.30)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>266 (59.9)</td>
</tr>
<tr>
<td><strong>Marital status, n (%)</strong></td>
<td>286 (64.0)</td>
</tr>
<tr>
<td><strong>Employment status, n (%)</strong></td>
<td>270 (61.4)</td>
</tr>
<tr>
<td><strong>Years of education, mean (s.d.)</strong></td>
<td>13.77 (2.71)</td>
</tr>
<tr>
<td><strong>Depression:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Kessler Distress 10 score, mean (s.d.)</strong></td>
<td>17.29 (5.36)</td>
</tr>
<tr>
<td><strong>PHQ–9 depression score, mean (s.d.)</strong></td>
<td>5.37 (4.21)</td>
</tr>
<tr>
<td><strong>PHQ–9 depression score &gt;10, n (%)</strong></td>
<td>380 (5.0)</td>
</tr>
<tr>
<td><strong>PHQ–9 depression score &gt;10–14, n (%)</strong></td>
<td>48 (0.7)</td>
</tr>
<tr>
<td><strong>PHQ–9 depression score &gt;15–19, n (%)</strong></td>
<td>14 (0.3)</td>
</tr>
<tr>
<td><strong>PHQ–9 depression score &gt;20, n (%)</strong></td>
<td>5 (0.1)</td>
</tr>
<tr>
<td><strong>Count of medical conditions, mean (s.d.)</strong></td>
<td>1.53 (1.19)</td>
</tr>
<tr>
<td><strong>Mental health exposure, mean (s.d.)</strong></td>
<td>10.04 (3.01)</td>
</tr>
</tbody>
</table>

a. Comparisons for each intervention arm are averaged over other arms.
b. \( P \) values are based on \( F \) statistics for continuous variables and \( \chi^2 \) statistics for categorical variables.
c. Patient Health Questionnaire (PHQ) severity categories include: minimal/mild (0–9); moderate (10–14); 15–19 (moderately severe); severe (>20).26
undertook a secondary analysis excluding individuals with high parameters, vitamin B12 and red cell folate levels were assessed. There were no significant adverse events related directly to the intervention in the randomised controlled trial (RCT) from their nominated healthcare provider due to markedly elevated gamma-glutamyltransferase (γ-GT) (1350 u/l) and thyroid-stimulating hormone (198.0 μu/l) levels, respectively. There were no differences in self-reported adverse events between the folic acid + B12 intervention and placebo groups at baseline or after follow-up assessments, except at 6 weeks when placebo participants reported significantly more side-effects than folate participants (F(1,898) = 4.58, P = 0.033). Nineteen participants withdrew from the intervention citing ill health. Two participants died during the 24-month period with both receiving the placebo tablet. Fifteen participants required further assessment and monitoring for potential suicidality; however, no participants withdrew because of depression.

### Safety and adverse events

There were no significant adverse events related directly to the study. Thyroid, liver and kidney function, haematological parameters, vitamin B12 and red cell folate levels were assessed by Capital Pathology (part of Sonic Health Care Ltd) at baseline, 12 and 24 months. At the 24-month assessment, two participants required urgent follow-up treatment (unrelated to their participation in the randomised controlled trial (RCT) from their nominated healthcare provider due to markedly elevated gamma-glutamyltransferase (γ-GT) (1350 u/l) and thyroid-stimulating hormone (198.0 μu/l) levels, respectively. There were no differences in self-reported adverse events between the folic acid + B12 intervention and placebo groups at baseline or follow-up assessments, except at 6 weeks when placebo participants reported significantly more side-effects than folate participants (F(1,898) = 4.58, P = 0.033). Nineteen participants withdrew from the intervention citing ill health. Two participants died during the 24-month period with both receiving the placebo tablet. Fifteen participants required further assessment and monitoring for potential suicidality; however, no participants withdrew because of depression.

### Discussion

#### Main findings

In this study of symptomatic community-dwelling participants, none of the interventions as planned, i.e. mental health literacy, folic acid + vitamin B12 supplementation and promoting physical activity, were effective in reducing depressive symptoms relative to their comparators at 24 months. Post hoc analyses indicated that only those who received the mental health literacy intervention experienced a significant decrease in depressive symptoms at 6 weeks relative to the control condition (d = 0.15, with control for covariates). This finding may indicate that promoting mental health literacy is effective in the short term. However, this effect may be due to a type 1 error since the effect was brief and the magnitude small. Moreover, we are reluctant to weigh it too strongly given that our analysis was post hoc. Interestingly, a recent meta-analysis reported that passive education (or mental health literacy) can produce significant effects on depression symptoms (r(865) = −0.75, P = 0.080, effect size d = 0.09). Subsequent effects of mental health literacy, although still in the same direction, were not significant. Figure 2 shows the mean PHQ–9 depression scores for each intervention arm.

More comprehensive models were also examined, controlling for the effects of age, gender, years of education, marital status, employment status, count of medical conditions, history of vascular conditions, mental illness exposure and K10 distress score at screening. These models yielded similar results. Most importantly, the significant effect for the mental health literacy intervention at 6 weeks was maintained after controlling for these potential confounders (r(865) = −2.43, P = 0.015). We also undertook a secondary analysis excluding individuals with high K10 scores (i.e. >24); the same findings resulted.

#### Table 2: Mixed-model parameters, significance and confidence intervals for Patient Health Questionnaire (PHQ) depression

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>s.e.</th>
<th>t</th>
<th>P</th>
<th>95% CI</th>
<th>Effect size, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>5.195</td>
<td>0.284</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Folate interventiona</td>
<td>0.214</td>
<td>0.283</td>
<td>0.756</td>
<td>0.450</td>
<td>−0.341 to 0.769</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>0.140</td>
<td>0.283</td>
<td>0.496</td>
<td>0.620</td>
<td>−0.415 to 0.696</td>
<td></td>
</tr>
<tr>
<td>Mental health literacy</td>
<td>0.199</td>
<td>0.283</td>
<td>0.703</td>
<td>0.482</td>
<td>−0.356 to 0.754</td>
<td></td>
</tr>
<tr>
<td>Wave</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baselineb</td>
<td>6 weeks</td>
<td>−1.033</td>
<td>0.243</td>
<td>−4.244</td>
<td>&lt;0.001</td>
<td>1.511 to −0.555</td>
</tr>
<tr>
<td>6 months</td>
<td>−0.193</td>
<td>0.271</td>
<td>−0.710</td>
<td>0.478</td>
<td>−0.725 to 0.340</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>−1.021</td>
<td>0.291</td>
<td>−3.511</td>
<td>&lt;0.001</td>
<td>1.592 to −0.450</td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td>−1.350</td>
<td>0.296</td>
<td>−4.557</td>
<td>&lt;0.001</td>
<td>1.932 to −0.768</td>
<td></td>
</tr>
<tr>
<td>Folate x wave</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Folate x baselinec</td>
<td>6 weeks</td>
<td>−0.065</td>
<td>0.242</td>
<td>−0.268</td>
<td>0.789</td>
<td>−0.540 to 0.410</td>
</tr>
<tr>
<td>Folate x 6 months</td>
<td>−0.399</td>
<td>0.270</td>
<td>−1.334</td>
<td>0.183</td>
<td>−0.889 to 0.170</td>
<td></td>
</tr>
<tr>
<td>Folate x 12 months</td>
<td>−0.031</td>
<td>0.290</td>
<td>−0.106</td>
<td>0.916</td>
<td>−0.600 to 0.538</td>
<td></td>
</tr>
<tr>
<td>Folate x 24 months</td>
<td>0.043</td>
<td>0.298</td>
<td>0.145</td>
<td>0.885</td>
<td>−0.542 to 0.628</td>
<td></td>
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<tr>
<td>Physical activity x wave</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity x baselineg</td>
<td>6 weeks</td>
<td>−0.029</td>
<td>0.242</td>
<td>−0.119</td>
<td>0.905</td>
<td>−0.504 to 0.446</td>
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<tr>
<td>Physical activity x 6 months</td>
<td>−0.434</td>
<td>0.270</td>
<td>−1.610</td>
<td>0.108</td>
<td>−0.963 to 0.095</td>
<td></td>
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<tr>
<td>Physical activity x 12 months</td>
<td>0.095</td>
<td>0.327</td>
<td>0.374</td>
<td>0.714</td>
<td>−0.474 to 0.664</td>
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<tr>
<td>Physical activity x 24 months</td>
<td>0.232</td>
<td>0.298</td>
<td>0.780</td>
<td>0.435</td>
<td>−0.352 to 0.817</td>
<td></td>
</tr>
<tr>
<td>Mental health literacy x wave</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health literacy x baselineg</td>
<td>6 weeks</td>
<td>−0.551</td>
<td>0.242</td>
<td>−2.276</td>
<td>0.023</td>
<td>−1.026 to −0.076</td>
</tr>
<tr>
<td>Mental health literacy x 6 months</td>
<td>−0.462</td>
<td>0.270</td>
<td>−1.714</td>
<td>0.087</td>
<td>−0.991 to 0.067</td>
<td></td>
</tr>
<tr>
<td>Mental health literacy x 12 months</td>
<td>−0.332</td>
<td>0.290</td>
<td>−1.144</td>
<td>0.253</td>
<td>−0.990 to 0.237</td>
<td></td>
</tr>
<tr>
<td>Mental health literacy x 24 months</td>
<td>−0.323</td>
<td>0.298</td>
<td>−1.084</td>
<td>0.279</td>
<td>−0.908 to 0.262</td>
<td></td>
</tr>
</tbody>
</table>

a. Degrees of freedom range from 824 to 896.
b. Reference category is placebo or comparator intervention.
c. Reference category.

(©(865) = −1.75, P = 0.080, effect size d = 0.09). Subsequent effects of mental health literacy, although still in the same direction, were not significant. Figure 2 shows the mean PHQ–9 depression scores for each intervention arm.
analyses showed large increases in blood levels of folate and vitamin B₁₂ in those receiving the active tablet. This finding does not preclude an effect at higher doses than used in this trial.

There is a difficulty characterising our results as evidence of either treatment or prevention of a depressive disorder. Our main finding that participants in the mental health literacy intervention experienced a significant decrease in depressive symptoms at 6 weeks relative to the control condition is subject to a difficult nosological issue. It could be argued that the Beyond Ageing Project is a treatment RCT as mental health literacy resulted in a short-term reduction in depressive symptoms compared with the control. However, the study can be appropriately defined as a non-specific effect of contact with interviewers even though 43% of the participants responded that the telephone contact with interviewers was an important component of the intervention and 90% reported that the telephone interviews were needed to remain engaged with the study.

Based on screening cut-off scores provided by the K10, we know that most of the participants (i.e. 91%) were at low to medium risk of having a depressive or anxiety disorder at the time of screening (K10 scores 16–30). We judged that 58% of participants had a low probability (3% or less) of meeting DSM–IV criteria for an affective disorder. Ideally, trials should incorporate telephone-based diagnosis to identify those meeting criteria for a depressive disorder. However, this will often be incompatible with the sample sizes required to detect preventive effects.

There is a difficulty characterising our results as evidence of either treatment or prevention of a depressive disorder. Our main finding that participants in the mental health literacy intervention experienced a significant decrease in depressive symptoms at 6 weeks relative to the control condition is subject to a difficult nosological issue. It could be argued that the Beyond Ageing Project is a treatment RCT as mental health literacy resulted in a short-term reduction in depressive symptoms compared with the control. However, the study can be appropriately defined as
a prevention trial given that depression prevention programmes may target numerous risk factors including high levels of psychological distress.47

**Strengths and limitations**

This is one of the largest trials to date to examine the effectiveness of psychological- and lifestyle-based preventive interventions for a high-risk group of community-dwelling older adults with psychological distress. The study was well executed and participants were engaged. The interventions chosen were acceptable, safe, low cost and accessible. The drop-out rate from randomisation to the 24-month assessment of 13.5% (82.7% of participants randomised into the RCT completed the 2-year intervention) was remarkably low relative to other psychosocial and lifestyle-based intervention trials for depression that report drop-out rates of 10–23%,9,14 with all except one14 involving brief interventions with less than 3 months duration. Unlike many studies executed in clinical settings, the present study delivered the interventions in a real-world setting despite stringent exclusion criteria due to ethical considerations.

The study had the limitation, however, that of the 24 352 older adults who returned their surveys, only 909 (3.8%) met the criteria or agreed to participate in the intervention. Although this may appear to be a low recruitment rate, the trial was unique in attempting to ascertain participants from a defined population sampling frame. This approach necessarily targets a large number of individuals who ultimately do not qualify for inclusion. However, bypassing conventional means of recruitment such as advertising and actively, and individually, soliciting participants is likely to have resulted in the inclusion of individuals who may not have recognised their at-risk status or been reluctant to seek assistance from healthcare professionals.

In the development of the trial, it was difficult to determine whether our original sample size target would be achieved given that few community-based interventions of this scale have been conducted. We anticipated recruiting 2000 people based on prevalence rates for this age group and on our experience of previous recruitment rates for community samples. However, there were issues that impinged on our trial that made the participation rate lower than expected. For example, many participants may have been unable to commit to a 2-year programme. Our target group was older than previous trials and may have had issues that impinged on our trial that made the participation rate lower than expected. For example, many participants may have been unable to commit to a 2-year programme. Our target group was older than previous trials and may have had issues that impinged on our trial that made the participation rate lower than expected. For example, many participants may have been unable to commit to a 2-year programme. Our target group was older than previous trials and may have had issues that impinged on our trial that made the participation rate lower than expected. For example, many participants may have been unable to commit to a 2-year programme.

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**Implications**

None of the interventions were effective in reducing depressive symptoms at 24 months compared with their respective comparators. However, our study suggests that there may be a role for brief mental health literacy interventions in reducing depressive symptoms, at least over short periods of time. Mental health literacy interventions are inexpensive and their indicated preventive effect may be worthwhile if provided to large numbers of older community-dwelling people with distress and, particularly, if the resultant literacy could be harnessed to encourage subsequent evidence-based treatment. Further investigation is needed to determine the appropriate dose–response levels of folic acid and vitamin B12 supplementation, if there are indeed any, for managing depressive symptoms in older adults. However, the prospect of using these dietary supplements at acceptable dosages as a preventive strategy for older people with psychological distress seems limited.

**References**


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