Mental health literacy, folic acid and vitamin B$_{12}$, 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 B$_{12}$ reduce depression symptoms in community-dwelling older adults with elevated psychological distress.

Method
An RCT with a completely crossed $2 \times 2 \times 2$ factorial design: (400 mcg/d folic acid + 100 mcg/d vitamin B$_{12}$ 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 + B$_{12}$ ($F(3,856) = 0.83$, $P = 0.476$) 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 B$_{12}$ 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.[1] 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.[6] 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 B$_{12}$ may reduce or prevent depression.[14,15] Folic acid and vitamin B$_{12}$ 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 B$_{12}$ have been found in community samples of adults with depression[16] although the evidence is uncertain whether folate and vitamin B$_{12}$ offer effective treatment for depression.[17] Supplementary folic acid and vitamin B$_{12}$ 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 B$_{12}$ as preventive interventions for an older population with elevated psychological distress. A factorial 2 (folic acid + vitamin B$_{12}$, placebo) × 2 (physical activity promotion, control) × 2 (mental health literacy, control) design was chosen. This design had the advantage of testing multiple inventions 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'.[19] 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.[20] 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)[21] 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 $2 \times 2 \times 2$ factorial design reflected the three interventions and their matched control interventions. Participants were randomised into 1 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.[24] 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,[28] 26 participants withdrew from the study, and 72 participants stopped taking the

tablets because of concerns relating to the information we provided regarding safety and the changes in the protocol for administrating the tablets. Adherence was monitored by telephone assessments (6 weeks, 6, 12 and 24 months) and ten brief telephone calls (1–5 weeks, and 4, 8, 13, 18 and 22 months) during which participants were requested to count the left over tablets and also by measurement of blood assay at baseline, 12- and 24-month assessments.

Placebo. Placebo tablets were manufactured by the same producers of the folic acid + vitamin B_{12} tablets and were identical except for the omission of the active substances under investigation.

Physical activity promotion arm

Physical activity promotion. This included a printed manual that was a targeted intervention based on the participant's stage of change,[29] and a pedometer (Digi-Walker SW-700, Yamax Inc, Tokyo, Japan).[30] The manual's content was informed by social cognitive theory and the transtheoretical model,[31] and contained evidence-based strategies to promote greater physical activity levels. Five newsletters including information on physical activity and local resources were delivered at 4, 8, 13, 18 and 22 months.

Nutrition promotion. This consisted of an evidence-based nutrition manual[32] on the dietary requirements of older adults (modules 1–5). Modules 6–10 included additional information and strategies to promote positive eating habits.

Measures

Demographic, physical and mental health

Age, gender, years of education, marital and employment status were ascertained. A checklist identified vascular disease and other health problems,[33] and side-effects potentially associated with folic acid + B_{12} supplementation were monitored with a modified version of the Liverpool University Neuroleptic Side Effect Rating Scale.[34] The K10 was selected as a screening tool to identify individuals with elevated psychological distress (anxiety and depression) because of its brevity and community use.[35] A modified version of the Level of Contact Report examined exposure to depression.[36] This survey lists 12 situations in which intimacy of contact with severe mental illness varies.

Outcome measures

Depressive symptoms and physical activity outcomes were assessed at baseline, 6 weeks (within 1 week of this time frame), 6, 12 and 24 (all within 2 weeks of this time frame).

Depressive symptoms. The Patient Health Questionnaire (PHQ–9) is a diagnostic tool specific to depression,[37,38] and hence was used as the primary outcome measure.

Physical activity. The International Physical Activity Questionnaire – Short Form (IPAQ–SF)[22] was used as a self-report measure of physical activity.

Folate, vitamin B_{12} and homocysteine concentration in blood. Serum vitamin B_{12}, red cell folate and homocysteine were measured at baseline and at the 12- and 24-month assessments to determine adherence, and homocysteine provided a measure of metabolic bioefficacy of folic acid + vitamin B_{12} supplementation. A fluorescence polarisation immunoassay was used for the quantitative determination of total L-homocysteine in plasma (AxSYM, Abbott Laboratories, Abbott Park, Illinois). Red cell folate and serum vitamin B_{12} were measured using chemiluminscent microparticle assays (Architect i2000, Abbott Laboratories).

Sample size and power

Power calculations led to an initial target sample size of 2000. This would have enabled the detection of main effects of each intervention of 0.125 standard deviations with 80% power with $\alpha = 0.05$ assuming a pre–post-test correlation of 0.50. This sample size would also have given reasonable power to detect interactions between interventions. The rate of recruitment of participants meeting inclusion criteria prompted reconsideration of the target sample size. A final target of 1000 participants maintained power above 80% to detect main effects of 0.18 standard deviations, a value below the size of small effects. Although the power to detect interactions was compromised, the primary interest of the study lay in the effectiveness of each intervention rather than questions of synergies. From a total of 24 352 surveys received and screened, 909 participants met the study criteria and were randomised into one of eight intervention arms (Fig. 1).

Randomisation

Randomisation followed the screening assessment with block size fixed at eight and using strata comprising location, gender and high (19) and low (16–18) K10[21] depression scores (conducted by A.J.M.) using an automated computerised system. Further, 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 B_{12}, and placebo tablet bottles to ensure concealment of their content. Participants, interviewers, investigators and the survey administrators were masked to active intervention and folic 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.

Statistical methods

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.[39] 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 *v.* 14.42, $F = 1023.46$,

Screening mail out
(*n* = 105 000)

↓

Assessed for eligibility
(*n* = 24 352)

→ Excluded
(*n* = 23 443)

Not meeting inclusion criteria
(*n* = 14 684)

Declined to participate
(*n* = 8740)

↓

Randomised
(*n* = 909)

Baseline Completed (*n* = 900)

Folate + B₁₂ tablet, nutrition, pain info
Allocated to intervention (*n* = 114)
Received intervention (*n* = 111)
Did not receive intervention (*n* = 3)
Reasons: non-contactable, moved, refused tablets
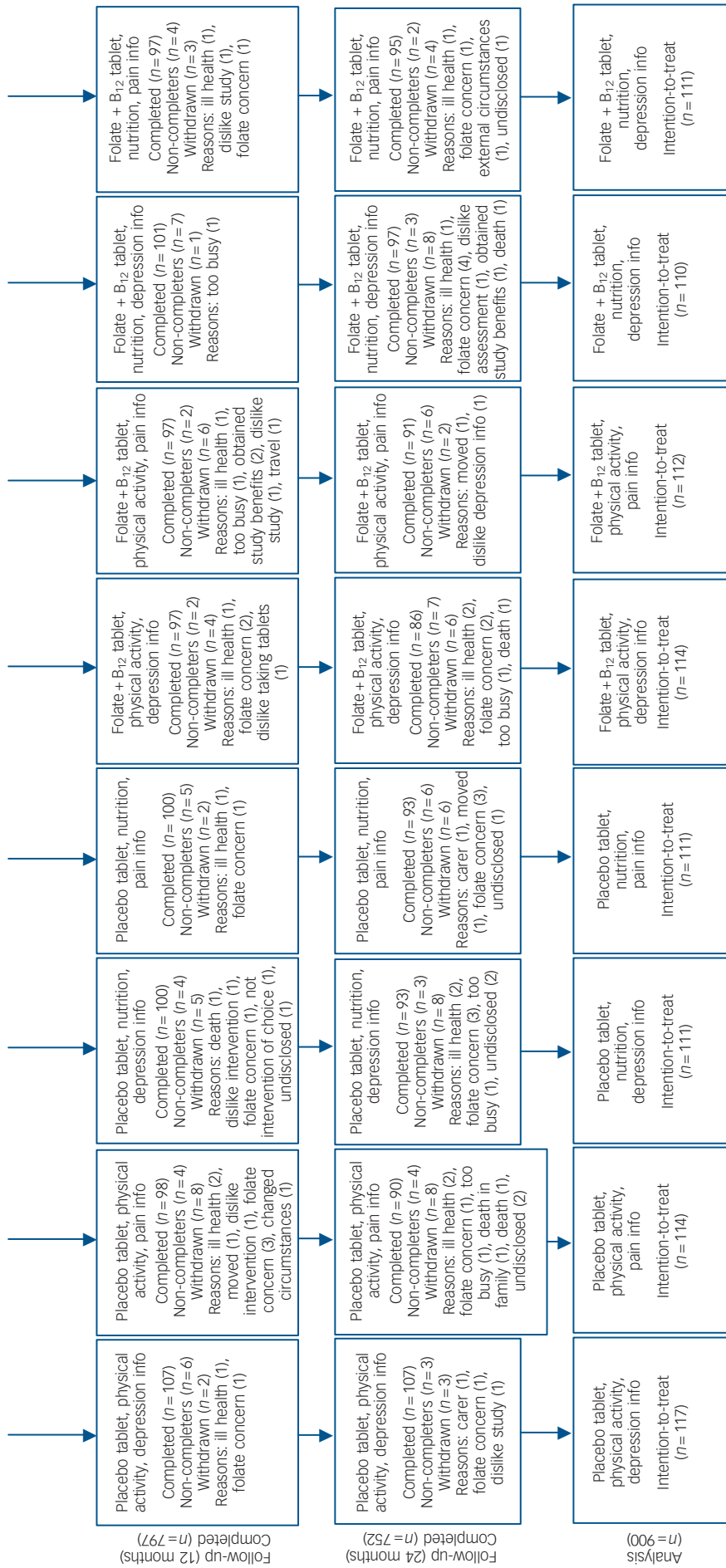
Folate + B₁₂ tablet, nutrition, depression info
Allocated to intervention (*n* = 112)
Received intervention (*n* = 110)
Did not receive intervention (*n* = 2)
Reasons: non-contactable, ill health

Folate + B₁₂ tablet, physical activity, pain info
Allocated to intervention (*n* = 113)
Received intervention (*n* = 112)
Did not receive intervention (*n* = 1)
Reasons: moved

Folate + B₁₂ tablet, physical activity, depression info
Allocated to intervention (*n* = 114)
Received intervention (*n* = 114)
Did not receive intervention (*n* = 0)
Reasons: n/a

Placebo tablet, nutrition, pain info
Allocated to intervention (*n* = 112)
Received intervention (*n* = 111)
Did not receive intervention (*n* = 1)
Reasons: incomplete

Placebo tablet, nutrition, depression info
Allocated to intervention (*n* = 112)
Received intervention (*n* = 111)
Did not receive intervention (*n* = 1)
Reasons: non-contactable

Placebo tablet, physical activity, pain info
Allocated to intervention (*n* = 115)
Received intervention (*n* = 114)
Did not receive intervention (*n* = 1)
Reasons: non-contactable

Placebo tablet, physical activity, depression info
Allocated to intervention (*n* = 117)
Received intervention (*n* = 117)
Did not receive intervention (*n* = 0)
Reasons: n/a

Follow-up (6 weeks) Completed (*n* = 855)

Folate + B₁₂ tablet, nutrition, pain info
Completed (*n* = 103)
Non-completers (*n* = 6)
Withdrawn (*n* = 2)
Reasons: ill health (2), moved (1), disliked assessment (1), family (1), travel (1)

Folate + B₁₂ tablet, nutrition, depression info
Completed (*n* = 106)
Non-completers (*n* = 3)
Withdrawn (*n* = 1)
Reasons: did not get preferred treatment (1)

Folate + B₁₂ tablet, physical activity, pain info
Completed (*n* = 107)
Non-completers (*n* = 1)
Withdrawn (*n* = 4)
Reasons: perceived tablet effect (2), unable to contact (2)

Folate + B₁₂ tablet, physical activity, depression info
Completed (*n* = 105)
Non-completers (*n* = 5)
Withdrawn (*n* = 4)
Reasons: ill health (2), moved (1), work (1)

Placebo tablet, nutrition, pain info
Completed (*n* = 105)
Non-completers (*n* = 4)
Withdrawn (*n* = 2)
Reasons: dislike study (1), perceived tablet effect (1)

Placebo tablet, nutrition, depression info
Completed (*n* = 106)
Non-completers (*n* = 4)
Withdrawn (*n* = 1)
Reasons: dislike assessment (1)

Placebo tablet, physical activity, pain info
Completed (*n* = 108)
Non-completers (*n* = 4)
Withdrawn (*n* = 2)
Reasons: dislike study (1), death (1)

Placebo tablet, physical activity, depression info
Completed (*n* = 115)
Non-completers (*n* = 1)
Withdrawn (*n* = 1)
Reasons: carer (1)

Follow-up (6 months) Completed (*n* = 825)

Folate + B₁₂ tablet, nutrition, pain info
Completed (*n* = 100)
Non-completers (*n* = 4)
Withdrawn (*n* = 1)
Reasons: dislike taking tablets (1)

Folate + B₁₂ tablet, nutrition, depression info
Completed (*n* = 105)
Non-completers (*n* = 4)
Withdrawn (*n* = 0)
Reasons: n/a

Folate + B₁₂ tablet, physical activity, pain info
Completed (*n* = 98)
Non-completers (*n* = 7)
Withdrawn (*n* = 3)
Reasons: ill health (2), dislike assessments (1)

Folate + B₁₂ tablet, physical activity, depression info
Completed (*n* = 101)
Non-completers (*n* = 2)
Withdrawn (*n* = 7)
Reasons: ill health (2), bored with treatment (1), dislike study (1), depression info not relevant (1), work (1), perceived tablet effect (1)

Placebo tablet, nutrition, pain info
Completed (*n* = 106)
Non-completers (*n* = 1)
Withdrawn (*n* = 2)
Reasons: ill health (1), materials not effective (1)

Placebo tablet, nutrition, depression info
Completed (*n* = 107)
Non-completers (*n* = 2)
Withdrawn (*n* = 1)
Reasons: ill health (1)

Placebo tablet, physical activity, pain info
Completed (*n* = 105)
Non-completers (*n* = 5)
Withdrawn (*n* = 2)
Reasons: perceived tablet effect (2)

Placebo tablet, physical activity, depression info
Completed (*n* = 103)
Non-completers (*n* = 12)
Withdrawn (*n* = 1)
Reasons: ill health (1)

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.

$P = 0.001$). More were taking prescribed antidepressant medication (16.5% v. 8.3%, $\chi^2 = 71.82.00$, $P = 0.001$), as well as being younger (mean 65.94 years v. 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% v. 25.10%; $\chi^2 = 11.98$, $P = 0.007$), as well as engaged in paid employment (34.3% v. 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 v. 65.94 years, $F = 35.71$, $P = 0.001$), reported fewer years of education (mean 11.78 v. 13.85, $F = 160.55$, $P = 0.001$), and by the nature of the study criteria had significantly higher K10 scores (mean 35.18 v. 20.43, $F = 2735.78$, $P = 0.001$), with more taking prescribed antidepressant medication (42.7% v. 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 + B_{12} 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 + B_{12} v. placebo: $\chi^2(1) = 0.6$, $P = 0.42$; physical activity v. nutrition

promotion: $\chi^2(1) = 2.0$, $P = 0.16$; mental health literacy v. pain information: $\chi^2(1) = 0.6$, $P = 0.44$).

Folic acid + vitamin B_{12} and physical activity levels

Relative to placebo, the folic acid + B_{12} group experienced a significant folate increase (from 573 to 951 nmol/l; $t(690) = 12.0$, $P < 0.001$) and B_{12} levels (from 305 to 475 nmol/l, $t(681) = 14.5$, $P < 0.0001$) over the 24-month period. Homocysteine increased significantly less in the folic acid + B_{12} 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 × intervention arm effects were not significant for folic acid + B_{12} ($F(3,856) = 0.83$, $P = 0.476$), 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 1 Baseline participant characteristics for each treatment group[a]

	Folic acid + B_{12}			Physical activity			Mental health literacy		
	Folic acid + B_{12} ($n = 447$)	Folic acid + B_{12} placebo ($n = 453$)	P^b	Physical activity ($n = 457$)	Physical activity control (nutrition) ($n = 443$)	P^b	Mental health literacy ($n = 452$)	Mental health literacy control (pain management) ($n = 448$)	P^b
Age, years: mean (s.d.)	65.92 (4.30)	65.97 (4.18)	0.861	66.20 (4.41)	65.68 (4.04)	0.065	66.10 (4.30)	65.78 (4.17)	0.250
Female, n (%)	266 (59.5)	276 (60.9)	0.664	277 (60.6)	265 (59.8)	0.808	270 (59.7)	272 (60.7)	0.764
Marital status, n (%)									
Married/de-facto	286 (64.0)	278 (61.4)	0.119	290 (63.5)	274 (61.9)	0.169	284 (62.8)	280 (62.5)	0.952
Separated/divorced	86 (19.2)	75 (16.6)		90 (19.7)	71 (16.0)		83 (18.4)	78 (17.4)	
Widowed	51 (11.4)	59 (16.6)		49 (10.7)	61 (13.8)		54 (11.9)	56 (12.5)	
Never married	24 (5.4)	41 (9.1)		28 (6.1)	37 (8.4)		31 (6.9)	34 (7.6)	
Employment status, n (%)									
Not in the labour force	270 (61.4)	289 (64.9)	0.117	298 (65.9)	261 (60.3)	0.221	288 (65.2)	271 (61.2)	0.353
Employed full time	72 (16.4)	50 (11.2)		61 (13.5)	61 (14.1)		63 (14.3)	59 (13.3)	
Employed part time	90 (20.5)	91 (20.4)		82 (18.1)	99 (22.9)		83 (18.8)	98 (22.1)	
Unemployed, looking for work	8 (1.8)	15 (3.4)		11 (2.4)	12 (2.8)		8 (1.8)	15 (3.4)	
Years of education, mean (s.d.)	13.77 (2.71)	13.92 (2.86)	0.407	13.81 (2.86)	13.89 (2.72)	0.656	13.83 (2.76)	13.86 (2.82)	0.876
Depression[c]									
Kessler Distress 10 score, mean (s.d.)	17.29 (5.36)	17.56 (5.15)	0.438	17.34 (5.33)	17.52 (5.18)	0.603	17.31 (5.23)	17.54 (5.28)	0.499
PHQ–9 depression score, mean (s.d.)	5.37 (4.21)	5.58 (4.27)	0.448	5.54 (4.29)	5.40 (4.19)	0.614	5.57 (4.42)	5.37 (4.05)	0.479
PHQ–9 depression score (0–9), n (%)	380 (5.0)	373 (2.5)	0.204	380 (83.2)	373 (84.4)	0.577	374 (82.9)	379 (84.6)	0.478
PHQ–9 depression score (10–14), n (%)	48 (0.7)	59 (3.1)		53 (11.6)	54 (12.2)		53 (11.8)	54 (12.1)	
PHQ–9 depression score (15–19), n (%)	14 (3.1)	19 (4.2)		20 (4.4)	13 (2.9)		21 (4.7)	12 (2.7)	
PHQ–9 depression score ($\geqslant 20$), n (%)	5 (1.1)	1 (0.2)		4 (0.9)	2 (0.5)		3 (0.7)	3 (0.7)	
Antidepressant use, n (%)	74 (16.6)	74 (16.4)	0.941	81 (17.8)	67 (15.2)	0.300	83 (18.4)	65 (14.5)	0.115
Health									
Count of medical conditions, mean (s.d.)	1.53 (1.19)	1.48 (1.13)	0.507	1.49 (1.18)	1.52 (1.13)	0.623	1.53 (1.19)	1.48 (1.12)	0.489
Have vascular condition, mean (s.d.)	0.71 (0.45)	0.75 (0.43)	0.162	0.73 (0.45)	0.74 (0.44)	0.807	0.74 (0.44)	0.73 (0.45)	0.760
Mental health exposure, mean (s.d.)	10.04 (3.01)	9.58 (3.27)	0.030	9.84 (3.21)	9.77 (3.10)	0.730	9.83 (3.19)	9.78 (3.12)	0.810

a. Comparisons for each intervention arm are averaged over other arms.
b. P values are based on F statistics for continuous variables and χ^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 ($\geqslant 20$).[38]

Table 2 Mixed-model parameters, significance and confidence intervals for Patient Health Questionnaire (PHQ) depression[a]

	Estimate	s.e.	t	P	95% CI	Effect size, d
Intercept	5.195	0.284				
Folate intervention[b]	0.214	0.283	0.756	0.450	−0.341 to 0.769	
Physical activity intervention	0.140	0.283	0.496	0.620	−0.415 to 0.696	
Mental health literacy intervention	0.199	0.283	0.703	0.482	−0.356 to 0.754	
Wave						
Baseline[c]						
6 weeks	−1.033	0.243	−4.244	<0.001	−1.511 to −0.555	
6 months	−0.193	0.271	−0.710	0.478	−0.725 to 0.340	
12 months	−1.021	0.291	−3.511	<0.001	−1.592 to −0.450	
24 months	−1.350	0.296	−4.557	<0.001	−1.932 to −0.768	
Folate × wave						
Folate × baseline[c]						
Folate × 6 weeks	−0.065	0.242	−0.268	0.789	−0.540 to 0.410	0.024
Folate × 6 months	−0.359	0.270	−1.334	0.183	−0.889 to 0.170	0.091
Folate × 12 months	−0.031	0.290	−0.106	0.916	−0.600 to 0.538	0.009
Folate × 24 months	0.043	0.298	0.145	0.885	−0.542 to 0.628	0.005
Physical activity × wave						
Physical activity × baseline[c]						
Physical activity × 6 weeks	−0.029	0.242	−0.119	0.905	−0.504 to 0.446	0.002
Physical activity × 6 months	−0.434	0.270	−1.610	0.108	−0.963 to 0.095	0.106
Physical activity × 12 months	0.095	0.290	0.327	0.743	−0.474 to 0.664	0.039
Physical activity × 24 months	0.232	0.298	0.780	0.435	−0.352 to 0.817	0.062
Mental health literacy × wave						
Mental health literacy × baseline[c]						
Mental health literacy × 6 weeks	−0.551	0.242	−2.276	0.023	−1.026 to −0.076	0.122
Mental health literacy × 6 months	−0.462	0.270	−1.714	0.087	−0.991 to 0.067	0.087
Mental health literacy × 12 months	−0.332	0.290	−1.144	0.253	−0.900 to 0.237	0.069
Mental health literacy × 24 months	−0.323	0.298	−1.084	0.279	−0.908 to 0.262	0.065

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

$(t(865) = -1.75, P = 0.080,$ 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.

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 $(t(865) = -2.43, P = 0.015)$. We also undertook a secondary analysis excluding individuals with high K10 scores (i.e. >24); the same findings resulted.

Safety and adverse events

There were no significant adverse events related directly to the study. Thyroid, liver and kidney function, haematological parameters, vitamin B_{12} 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 mu/l) levels, respectively. There were no differences in self-reported adverse events between the folic acid + B_{12} 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 B_{12} 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 suggesting replication is critical.[12]

An important outcome of the study was the failure to detect any effect of folic acid (400 mcg/d) + B_{12} (100 mcg/d) supplementation on reduction of depressive symptoms. This was unlikely to be as a result of adherence issues given that the biochemical
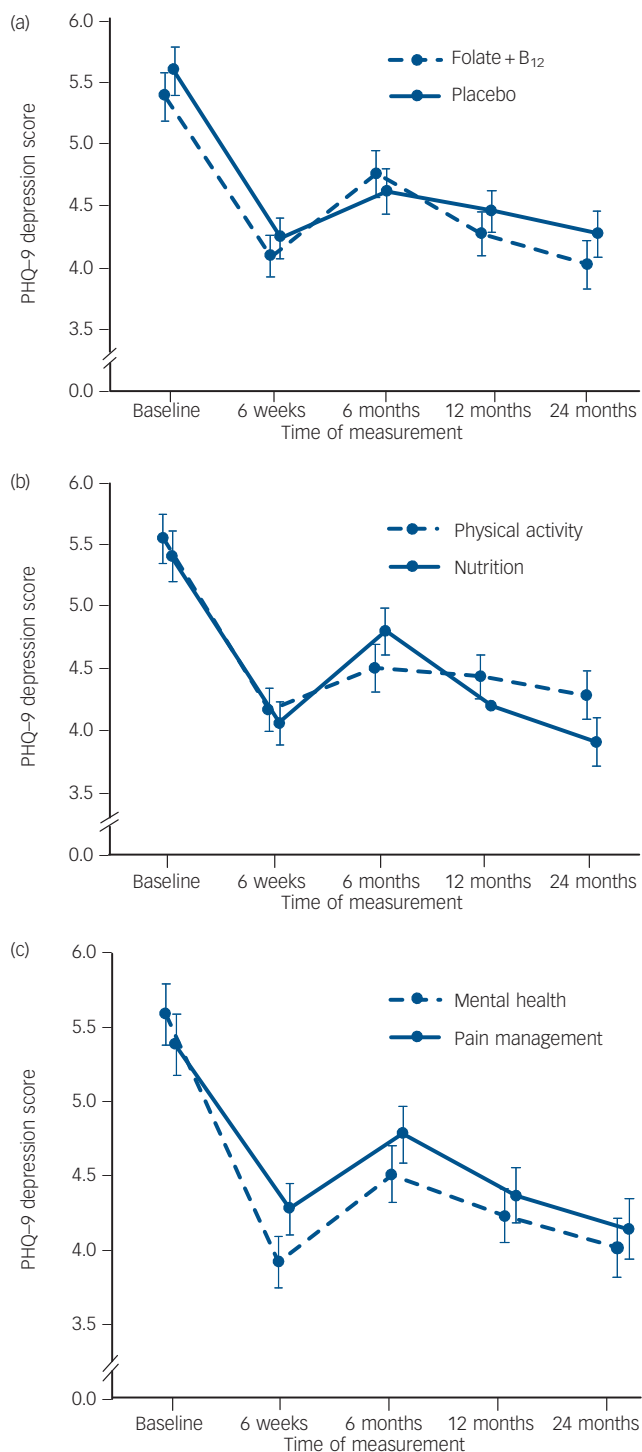
Fig. 2 Population marginal means of Patient Health Questionnaire (PHQ –9) depression score by treatment group. (a) Folate + B$_{12}$ *v.* placebo, (b) physical activity *v.* nutrition control, (c) mental health literacy *v.* pain management control.

Estimated population marginal means for the model shown in Table 2 are plotted in Fig. 2. Error bars represent standard error of the mean.

analyses showed large increases in blood levels of folate and vitamin B$_{12}$ in those receiving the active tablet. This finding does not preclude an effect at higher doses than used in this trial. Although the doses of folic acid and vitamin B$_{12}$ used in our study prevented further increase in homocysteine (as occurred in the placebo group) they appear to have been insufficient to lower homocysteine levels relative to baseline. Recent studies in the elderly (>70 years) suggest that >600 mcg/d vitamin B$_{12}$ may be required to reduce homocysteine and methylmalonic acid.[40] We therefore cannot exclude the possibility that the vitamin B$_{12}$ dose was too low for adequate bioefficacy even though it was 42 times greater than the Australian recommended dietary intake.[41] Use of higher folic acid doses was not possible because of ethical concerns relating to heightened colorectal cancer risk in otherwise asymptomatic elderly people.[28]

Randomised controlled trials have investigated a range of folate doses from 200 to 5000 mcg/day with varying findings.[17,18] Folic acid and vitamin B$_{12}$ are unlikely to be an effective short-term intervention for preventing depression in doses that can be recommended as a dietary supplement. The study replicates the null effect from an earlier, smaller and thus underpowered trial.[14] It is possible that such interventions need to be delivered over a longer period to reduce vascular and other metabolic risk factors to depression.[42]

The intervention to promote physical activity did not do so to a greater extent than the comparator invention. As a consequence, the hypothesis that physical activity would reduce depressive symptoms was not comprehensively tested. We cannot rule out the possibility that a different programme might have successfully promoted physical activity. However, our programme was rigorous and a good exemplar of a public health approach to promoting physical activity: it was developed in conjunction with consumer input and consideration of the current evidence base, especially for mediated delivery of physical activity interventions,[10] suggesting that significant changes would be needed for this approach to be effective. Similarly, a more intensive programme might be preventive, but this casts doubt on the likelihood of achieving this without substantial individual attention thus precluding widespread use.

All trial and control interventions were associated with a reduction in depressive symptoms (Cohen's $d = 0.32$, $F(4, 833.4) = 37.00$, $P < 0.001$) over 24 months. It is difficult to determine whether this reflected the course of depression over time, regression to the mean,[43] a non-specific effect of contact with the trial team[11] or because of engagement in community activities. Because trials without strong team support show similar trajectories,[44] it is unlikely to be as a result of the impact of the telephone 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[45] 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.[21,23] 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.[46] 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 one[14] 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 been reluctant to engage in scientific research. Also, we suspect that this group may have overestimated their activity levels, which resulted in many potential participants meeting exclusion criteria. Although the targeted recruitment rate was not met, the achieved sample would have detected small effects (down to approximately 0.2 standard deviations) under the original assumptions. It is possible that negative interactions may have reduced the efficiency of the trial but, in the absence of evidence of effects of individual interventions this is not likely to explain the failure to detect any benefit of exercise or folic acid and B_{12} supplementation.

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 B_{12} 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.

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First received 9 Nov 2009, final revision 5 Apr 2010, accepted 27 Apr 2010

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