Oral folic acid and vitamin B-12 supplementation to prevent cognitive decline in community-dwelling older adults with depressive symptoms—the Beyond Ageing Project: a randomized controlled trial[1–3]

Janine G Walker, Philip J Batterham, Andrew J Mackinnon, Anthony F Jorm, Ian Hickie, Michael Fenech, Marjan Kljakovic, Dimity Crisp, and Helen Christensen

ABSTRACT

Background: Evidence remains unclear as to whether folic acid (FA) and vitamin B-12 supplementation is effective in reducing depressive symptoms.

Objectives: The objective was to determine whether oral FA + vitamin B-12 supplementation prevented cognitive decline in a cohort of community-dwelling older adults with elevated psychological distress.

Design: A randomized controlled trial (RCT) with a completely crossed 2 × 2 × 2 factorial design comprising daily oral 400 μg FA + 100 μg vitamin B-12 supplementation (compared with placebo), physical activity promotion, and depression literacy with comparator control interventions for reducing depressive symptoms was conducted in 900 adults aged 60–74 y with elevated psychological distress (Kessler Distress 10–Scale; scores >15). The 2-y intervention was delivered in 10 modules via mail with concurrent telephone tracking calls. Main outcome measures examined change in cognitive functioning at 12 and 24 mo by using the Telephone Interview for Cognitive Status–Modified (TICS-M) and the Brief Test of Adult Cognition by Telephone (processing speed); the Informant Questionnaire on Cognitive Decline in the Elderly was administered at 24 mo.

Results: FA + vitamin B-12 improved the TICS-M total ($P = 0.032$; effect size $d = 0.17$), TICS-M immediate ($P = 0.046$; $d = 0.15$), and TICS-M delayed recall ($P = 0.013$; effect size $d = 0.18$) scores at 24 mo in comparison with placebo. No significant changes were evident in orientation, attention, semantic memory, processing speed, or informant reports.

Conclusion: Long-term supplementation of daily oral 400 μg FA + 100 μg vitamin B-12 promotes improvement in cognitive functioning after 24 mo, particularly in immediate and delayed memory performance. This trial was registered at clinicaltrials.gov as NCT00214682. *Am J Clin Nutr* 2012;95:194–203.

INTRODUCTION

Cognitive impairment is common in later life, with prevalence rates ranging from 2% to 29% (1, 2). It is associated with impaired neuropsychiatric, physical and social functioning, and reduced quality of life (3, 4) and predicts conversion to dementia (5). Effective prevention strategies are needed to protect individuals from decline or at least to minimize any adverse effects of cognitive impairment (6). A first step in the development of such programs is to identify interventions that prevent cognitive impairment in community-dwelling older adults (7). To date, the development and evaluation of such programs has been minimal.

One candidate intervention is oral FA[4] combined with vitamin B-12 supplementation. Two theories explain how such an intervention may prevent cognitive impairment and dementia. The first is by lowering homocysteine concentrations (8–10), whereas the second purports that supplementary FA and vitamin B-12 may operate by reducing vascular and other metabolic risk factors (9). To date, the strength of the evidence drawn from RCTs is equivocal with regard to the efficacy of FA and vitamin B-12 as a treatment of cognitive impairment or dementia (10–17). Systematic reviews of the literature indicate that trials involving cognitively impaired individuals who received a combination of vitamin B complex + FA supplements or FA alone showed improvements in memory, attention efficiency, motor speed, and visual conceptual and vasomotor tracking compared with control individuals (10, 18). However, less is known as to whether FA and vitamin B-12 supplementation is effective for

[1] From the Centre for Mental Health Research, Australian National University, Canberra, Australia (JGW, PJB, DC, and HC); ORYGEN Youth Health and The University of Melbourne, Melbourne, Australia (AJM and AFJ); the Brain and Mind Research Institute and The University of Sydney, Sydney, Australia (IH); the Nutrigenomics and Genome Health Laboratory, Commonwealth Scientific and Industrial Research Organisation, Adelaide, Australia (MF); and the Academic Unit of General Practice and Community Health, Medical School, Australian National University, Canberra, Australia (MK).

[2] Supported by beyondblue: the national depression initiative and the Australian Government Department of Health and Ageing. HC was supported by a National Health and Medical Research Council (NHMRC) fellowship no. 525411. JGW was supported by NHMRC Capacity Building Grant 418020.

[3] Address reprint requests and correspondence to JG Walker, Centre for Mental Health Research, Australian National University, Building 63, Eggleston Road, Acton, Australian Capital Territory, 0200 Australia. E-mail: janine.walker@anu.edu.au.

[4] Abbreviations used: BDNF, brain-derived neurotrophic factor; BTACT, Brief Test of Adult Cognition by Telephone; FA, folic acid; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; K10, Kessler Distress 10–Scale; RCT, randomized controlled trial; TICS-M, Telephone Interview for Cognitive Status–Modified.

Received November 14, 2010. Accepted for publication October 17, 2011.
First published online December 14, 2011; doi: 10.3945/ajcn.110.007799.

the prevention of negative cognitive changes, particularly in community-dwelling older adults (10, 19).

The present article reports a secondary analysis of the FA and vitamin B-12 (FA + vitamin B-12) supplementation intervention arising from a large-scale RCT designed primarily to investigate physical activity, mental health literacy, and FA + vitamin B-12 supplementation as preventive interventions for depression in an older population with elevated depressive symptoms (20). Those with elevated depressive symptoms are an important cohort to target because of evidence that late-life depression is associated with increased risk of cognitive impairment (21), with severe compared with mild depressive symptoms representing a greater risk of mild cognitive impairment (22).

We hypothesized that oral FA (400 μg/d) + vitamin B-12 (100 μg/d) supplementation would slow the rate of negative changes in cognitive function in a sample of community-dwelling individuals with elevated depression symptoms compared with placebo. Given the relative youth of our sample and the short follow-up time (24 mo), we expected only small negative cognitive changes to be observed. Indeed, it was possible that short-term increases in performance levels due to practice effects would be observed, because these are common in longitudinal studies in community-dwelling older adults (23). We predicted the extent of any negative changes (either a deterioration in performance levels, or a reduced improvement in performance due to practice effects) would be greater for individuals in the placebo condition than in those taking FA + vitamin B-12 supplementation.

SUBJECTS AND METHODS

Study design

The present study was an RCT that investigated potentially effective interventions for reducing depressive symptoms in older adults with a $2 \times 2 \times 2$ factorial design [(FA + vitamin B-12 supplementation compared with placebo tablet) $\times$ (physical activity promotion compared with comparator control, ie, information regarding nutrition for older adults) $\times$ (mental health literacy compared with comparator control, ie, pain and arthritis management information)]. Participants were randomly assigned to 1 of the 8 intervention programs arising from the combination of active or comparison conditions. The design and randomization process are reported elsewhere (20). Most outcomes were assessed at 5 time points: baseline, 6 wk, and 6, 12, and 24 mo. The cognitive functioning variables were assessed at baseline and at 12 and 24 mo.

Recruitment occurred between 22 October 2005 and 4 September 2006, with the 24-mo intervention and data collection occurring from 4 January 2006 to 18 September 2008. The 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.

Participants

The population-based sample was recruited by a direct mailing of a screening survey and consent form to 105,000 randomly selected adults aged from 60 to 74 y whose names, addresses, and dates of birth were obtained from the mail lists provided by the Australian Electoral Commission; the sample comprised federal electorates in 2 cities, Canberra (Australian Capital Territory) and Sydney, and a rural location, Wagga Wagga (New South Wales). It was anticipated that initially recruiting in this manner would yield an exhaustive and representative sample because electoral registration is mandatory in Australia. The screening survey addressed a number of factors relevant to the study including demographic and health information, physical activity participation, vitamin B and FA intake, and psychological distress and was scored by research assistants. Individuals who met these criteria were then asked to provide a blood sample in a community-based blood collection site (Sonic Health Care Ltd) for additional health data and to determine that red blood cell folate and vitamin B-12 concentrations were in a healthy range for ethical reasons. Selected participants had elevated psychological distress as assessed by the K10 (scores $\geq$16) (24); did not engage in physical activity at public health–recommended levels as indicated by International Physical Activity Questionnaire scores; did not take FA, 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 FA use. Individuals with high likelihood of a depressive disorder with K10 scores of $\geq$30 were excluded (25). Those individuals with low concentrations of red blood cell folate ($<$250 nmol/L) and vitamin B-12 ($<$130 nmol/L) and abnormal thyroid stimulating hormone concentrations (0.35–5.0 mU/L) were excluded because participation may have led to potentially adverse outcomes (20).

Interventions

Eligible participants were enrolled into an intervention program that was delivered over 24 mo in 10 modules. All interventions involved 5 brief telephone tracking calls over the first 5 wk and 5 more telephone calls at 4, 8, 13, 18, and 22 mo to ensure that the material and related tasks had been understood. With the exception of the FA + vitamin B-12 and placebo tablets, the first 5 modules of the interventions were delivered by mail during Weeks 1–5, followed by the remaining modules which were sent out at 4, 8, 13, 18, and 22 mo.

Dietary supplementation arm

FA + vitamin B-12 tablets were formulated as a daily oral dose of one tablet consisting of 400 μg FA and 100 μg vitamin B-12 (ABN57052101176; Matchland Pty Ltd) for the entire 24-mo period. After a safety review subsequent to a published RCT on the association between folate and colorectal adenomas (26), the protocol changed to 2 daily oral doses (200 μg FA + 50 μg vitamin B-12 each) from July 2007 (20). Adherence was monitored by telephone assessment at 14 time points and by blood assay at baseline and at 12- and 24-mo assessments.

Placebo tablets were manufactured by the same producers of the FA + vitamin B-12 tablets and were identical except for the omission of the active substances under investigation.

Demographic, physical, and mental health measures

Age, sex, years of education, and marital and employment status were established. A checklist identified vascular disease

and other health problems (27). The K10 was used to screen depression (28).

Study outcome measures

Cognitive function as well as concentrations of folate, vitamin B-12, and homocysteine were measured at baseline and at the 12- and 24-mo assessments.

Cognitive function was measured by using the TICS-M (29), which has a maximum total score of 39 and comprises 4 domains: *1*) orientation; *2*) registration, recent memory, and delayed recall; *3*) attention/calculation; and *4*) semantic memory, comprehension, and repetition. The TICS-M has a high proportion of the total score devoted to immediate and delayed recall, which affords it excellent discrimination in cognitive performance in the general population (29), and in the context of screening for dementia and mild cognitive impairment (30). Processing speed was measured by using the BTACT survey, which is a brief battery of key domains of cognitive function using tests that are sensitive to performance in community-dwelling adults ranging from young to middle-aged and older (31). Processing speed was measured with a backward-counting task in which the participant has 30 s to count backward quickly from 100 by ones. The total score represents the amount of numbers correctly reported in sequence, not counting errors (32). The reliability and validity of the BTACT has been shown to be good in community-dwelling samples, including in the elderly, with telephone administration yielding similar findings to usual in-person administration of standardized cognitive tests (32, 33).

The IQCODE was administered at 24 mo (34). It is a 26-item survey designed to measure cognitive decline and dementia in older adults. The questionnaire was completed by a relative or friend who had known the person for $\geq$2 y. The 5-point rating scale was designed to accommodate cognitive improvement as well as decline, with 1 indicating "much improved" to 5 indicating "much worse." Ratings were averaged to give a 1–5 score, with 3 representing no change (35). The IQCODE has excellent reliability and validity and had been used effectively in clinical settings and epidemiologic research and in conventional cognitive screening tests as a screening tool (35).

Serum vitamin B-12, red blood cell folate, and homocysteine were measured at baseline and at the 12- and 24-mo assessments. A fluorescence polarization immunoassay was used for the quantitative determination of total L-homocysteine in plasma (AxSYM; Abbott Laboratories). Red blood cell folate and serum vitamin B-12 were measured by using chemiluminescent microparticle assays (Architect i2000; Abbott Laboratories). These allowed a check on whether participants were taking the supplements and to establish a change in homocysteine concentration that was consistent with other studies showing a protective effect.

Depression was assessed at baseline, 6 wk (within 1 wk), and at 6, 12, and 24 mo (all within 2 wk). Depressive symptoms were measured by using the Patient Health Questionnaire–9 (36).

Randomization, sample size, power, and dropout

Randomization followed the screening assessment, with the block size fixed at 8 and with strata comprising location, sex, and high (scores $\geq$19) and low (scores of 16–18) K10 (24) depression scores, by using an automated computerized system (AJM). Stratification was used as part of the randomization process to ensure an even distribution of these variables across the intervention groups. Furthermore, the Internet site random.org was used (conducted by JGW) to randomly allocate a label "A" or "B" to the FA + 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.

The flow of participants through the study is shown in **Figure 1**. From a total of 105,000 screening surveys delivered, 24,352 surveys (ie, 23.19% of surveys were returned, whereas 80,648 individuals did not respond to the initial mail contact) were received and screened. Of the screening surveys received, 14,684 (62.64%) individuals failed to meet the criteria for inclusion. The primary reason for exclusion from the intervention was self-reported low levels of distress (72.30% had K10 scores $\geq$16). Of those, 909 (3.73%) participants wanted to participate in the intervention component of the study, met the study criteria, gave informed written consent, and were randomly assigned to 1 of 8 intervention combinations, with approximately half receiving FA + vitamin B-12 supplementation and the other half receiving the placebo. Calculations indicated that the sample size had 91% power to detect differences in treatment outcomes of 0.20 for the comparison of FA + vitamin B-12 with placebo, with an α of 0.05 (20).

Statistical analyses

Mixed-model repeated-measures ANOVA was used to evaluate hypotheses concerning differential change between FA + vitamin B-12 and the placebo. Multiple comparisons were not adjusted for when examining the TICS-M subscales and total score because hypotheses were determined a priori (37). Within-person variation was modeled by using an unstructured covariance matrix. df were estimated by using Satterthwaite's approximation (38). Models were developed for each of the cognitive outcome variables. The critical test of the effectiveness was the presence of an effect of the FA + vitamin B-12 supplementation relative to placebo over time—ie, showing that FA + vitamin B-12 supplementation improved cognitive functioning over time. Mixed models yield an intention-to-treat analysis by using all available measurement points for each participant under the assumption that withdrawal data are missing at random. Windows SPSS, version 15 (IBM Corporation), was used for all statistical analyses.

RESULTS

Demographic characteristics and dropout

Demographic differences at baseline are shown in **Table 1**. Those who received FA + vitamin B-12 had higher concentrations of serum vitamin B-12 than did those in the placebo group ($F_{1,898}$ = 5.33, P = 0.021). Of those who were recruited into the trial, the dropout rate was low, with only 123 (13.5%) participants withdrawing from the time of randomization to the 24-mo assessment. A total of 797 (87.7%) completed the 12-mo interview, and 752 (82.7%) completed the 24-mo interview. There were no significant differences in the proportions of

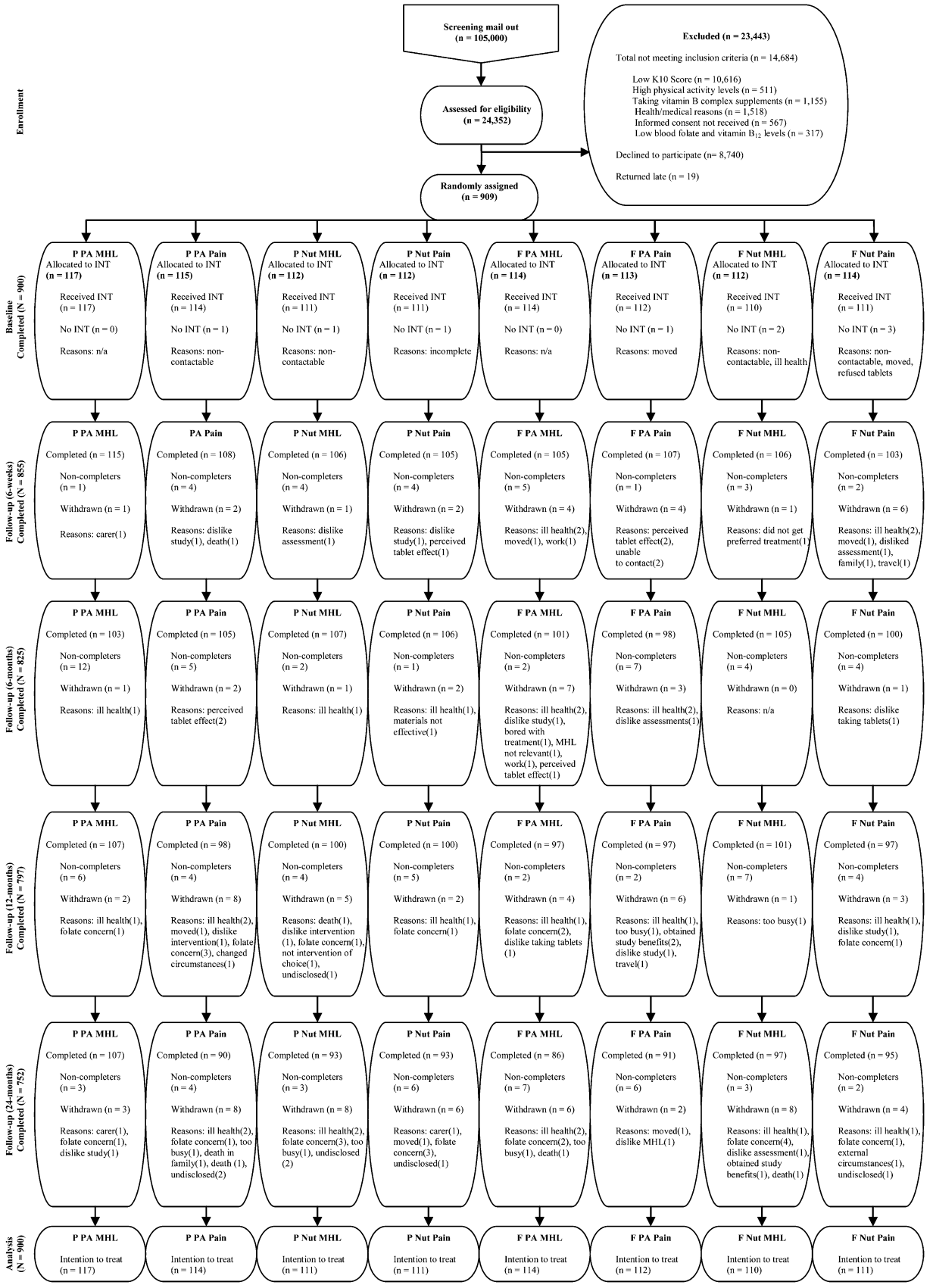
Enrollment
Screening mail out (n = 105,000)
Assessed for eligibility (n = 24,352)
Excluded (n = 23,443)
Total not meeting inclusion criteria (n = 14,684)
Low K10 Score (n = 10,616)
High physical activity levels (n = 511)
Taking vitamin B complex supplements (n = 1,155)
Health/medical reasons (n = 1,518)
Informed consent not received (n = 567)
Low blood folate and vitamin B12 levels (n = 317)
Declined to participate (n= 8,740)
Returned late (n = 19)
Randomly assigned (n = 909)
Baseline Completed (N = 900)
P PA MHL Allocated to INT (n = 117) | Received INT (n = 117) | No INT (n = 0) | Reasons: n/a
P PA Pain Allocated to INT (n = 115) | Received INT (n = 114) | No INT (n = 1) | Reasons: non-contactable
P Nut MHL Allocated to INT (n = 112) | Received INT (n = 111) | No INT (n = 1) | Reasons: non-contactable
P Nut Pain Allocated to INT (n = 112) | Received INT (n = 111) | No INT (n = 1) | Reasons: incomplete
F PA MHL Allocated to INT (n = 114) | Received INT (n = 114) | No INT (n = 0) | Reasons: n/a
F PA Pain Allocated to INT (n = 113) | Received INT (n = 112) | No INT (n = 1) | Reasons: moved
F Nut MHL Allocated to INT (n = 112) | Received INT (n = 110) | No INT (n = 2) | Reasons: non-contactable, ill health
F Nut Pain Allocated to INT (n = 114) | Received INT (n = 111) | No INT (n = 3) | Reasons: non-contactable, moved, refused tablets
Follow-up (6-weeks) Completed (N = 855)
P PA MHL Completed (n = 115) | Non-completers (n = 1) | Withdrawn (n = 1) | Reasons: carer(1)
PA Pain Completed (n = 108) | Non-completers (n = 4) | Withdrawn (n = 2) | Reasons: dislike study(1), death(1)
P Nut MHL Completed (n = 106) | Non-completers (n = 4) | Withdrawn (n = 1) | Reasons: dislike assessment(1)
P Nut Pain Completed (n = 105) | Non-completers (n = 4) | Withdrawn (n = 2) | Reasons: dislike study(1), perceived tablet effect(1)
F PA MHL Completed (n = 105) | Non-completers (n = 5) | Withdrawn (n = 4) | Reasons: ill health(2), moved(1), work(1)
F PA Pain Completed (n = 107) | Non-completers (n = 1) | Withdrawn (n = 4) | Reasons: perceived tablet effect(2), unable to contact(2)
F Nut MHL Completed (n = 106) | Non-completers (n = 3) | Withdrawn (n = 1) | Reasons: did not get preferred treatment(1)
F Nut Pain Completed (n = 103) | Non-completers (n = 2) | Withdrawn (n = 6) | Reasons: ill health(2), moved(1), disliked assessment(1), family(1), travel(1)
Follow-up (6-months) Completed (N = 825)
P PA MHL Completed (n = 103) | Non-completers (n = 12) | Withdrawn (n = 1) | Reasons: ill health(1)
P PA Pain Completed (n = 105) | Non-completers (n = 5) | Withdrawn (n = 2) | Reasons: perceived tablet effect(2)
P Nut MHL Completed (n = 107) | Non-completers (n = 2) | Withdrawn (n = 1) | Reasons: ill health(1)
P Nut Pain Completed (n = 106) | Non-completers (n = 1) | Withdrawn (n = 2) | Reasons: ill health(1), materials not effective(1)
F PA MHL Completed (n = 101) | Non-completers (n = 2) | Withdrawn (n = 7) | Reasons: ill health(2), dislike study(1), bored with treatment(1), MHL not relevant(1), work(1), perceived tablet effect(1)
F PA Pain Completed (n = 98) | Non-completers (n = 7) | Withdrawn (n = 3) | Reasons: ill health(2), dislike assessments(1)
F Nut MHL Completed (n = 105) | Non-completers (n = 4) | Withdrawn (n = 0) | Reasons: n/a
F Nut Pain Completed (n = 100) | Non-completers (n = 4) | Withdrawn (n = 1) | Reasons: dislike taking tablets(1)
Follow-up (12-months) Completed (N = 797)
P PA MHL Completed (n = 107) | Non-completers (n = 6) | Withdrawn (n = 2) | Reasons: ill health(1), folate concern(1)
P PA Pain Completed (n = 98) | Non-completers (n = 4) | Withdrawn (n = 8) | Reasons: ill health(2), moved(1), dislike intervention(1), folate concern(3), changed circumstances(1)
P Nut MHL Completed (n = 100) | Non-completers (n = 4) | Withdrawn (n = 5) | Reasons: death(1), dislike intervention (1), folate concern(1), not intervention of choice(1), undisclosed(1)
P Nut Pain Completed (n = 100) | Non-completers (n = 5) | Withdrawn (n = 2) | Reasons: ill health(1), folate concern(1)
F PA MHL Completed (n = 97) | Non-completers (n = 2) | Withdrawn (n = 4) | Reasons: ill health(1), folate concern(2), dislike taking tablets (1)
F PA Pain Completed (n = 97) | Non-completers (n = 2) | Withdrawn (n = 6) | Reasons: ill health(1), too busy(1), obtained study benefits(2), dislike study(1), travel(1)
F Nut MHL Completed (n = 101) | Non-completers (n = 7) | Withdrawn (n = 1) | Reasons: too busy(1)
F Nut Pain Completed (n = 97) | Non-completers (n = 4) | Withdrawn (n = 3) | Reasons: ill health(1), dislike study(1), folate concern(1)
Follow-up (24-months) Completed (N = 752)
P PA MHL Completed (n = 107) | Non-completers (n = 3) | Withdrawn (n = 3) | Reasons: carer(1), folate concern(1), dislike study(1)
P PA Pain Completed (n = 90) | Non-completers (n = 4) | Withdrawn (n = 8) | Reasons: ill health(2), folate concern(1), too busy(1), death in family(1), death (1), undisclosed(2)
P Nut MHL Completed (n = 93) | Non-completers (n = 3) | Withdrawn (n = 8) | Reasons: ill health(2), folate concern(3), too busy(1), undisclosed (2)
P Nut Pain Completed (n = 93) | Non-completers (n = 6) | Withdrawn (n = 6) | Reasons: carer(1), moved(1), folate concern(3), undisclosed(1)
F PA MHL Completed (n = 86) | Non-completers (n = 7) | Withdrawn (n = 6) | Reasons: ill health(2), folate concern(2), too busy(1), death(1)
F PA Pain Completed (n = 91) | Non-completers (n = 6) | Withdrawn (n = 2) | Reasons: moved(1), dislike MHL(1)
F Nut MHL Completed (n = 97) | Non-completers (n = 3) | Withdrawn (n = 8) | Reasons: ill health(1), folate concern(4), dislike assessment(1), obtained study benefits(1), death(1)
F Nut Pain Completed (n = 95) | Non-completers (n = 2) | Withdrawn (n = 4) | Reasons: ill health(1), folate concern(1), external circumstances(1), undisclosed(1)
Analysis (N = 900)
P PA MHL Intention to treat (n = 117)
P PA Pain Intention to treat (n = 114)
P Nut MHL Intention to treat (n = 111)
P Nut Pain Intention to treat (n = 111)
F PA MHL Intention to treat (n = 114)
F PA Pain Intention to treat (n = 112)
F Nut MHL Intention to treat (n = 110)
F Nut Pain Intention to treat (n = 111)

FIGURE 1. Flowchart of enrollment, randomization, and follow-up [on the basis of guidelines for RCTs of the CONSORT (CONsolidated Standards of Reporting Trials) statement]. From a total of 105,000 screening surveys delivered to community-dwelling older adults in Australia, 24,352 (23.19%) surveys were received and screened. Of those, 909 (3.73%) participants wanted to participate in the intervention component of the study, met the study criteria, provided informed written consent, and were randomly assigned to 1 of 8 intervention combinations, with approximately half receiving FA + vitamin B-12 supplementation and the other half receiving the placebo. A significant proportion of individuals (n = 8750, 35.93%) who returned the received surveys indicated on a specific item that they did not want to participate in the RCT. The dropout rate was low, with only 123 (13.5%) participants withdrawing from the time of random assignment to the 24-mo assessment. A total of 797 (87.7%) completed the 12-mo interview, and 752 (82.7%) completed the 24-mo interview. There were no significant differences in the proportions of participants who completed the 24-mo interview between the FA + vitamin B-12 and placebo groups (chi-square$_1$ = 0.6, P = 0.420). Completed, participants who completed the survey for that time point; FA, folic acid; F Nut MHL, folic acid + vitamin B-12 tablet, nutrition, mental health literacy; F Nut Pain, folic acid + vitamin B-12 tablet, nutrition, pain information; F PA MHL, folic acid + vitamin B-12 tablet, physical activity, mental health literacy; F PA Pain, folic acid + vitamin B-12 tablet, physical activity, pain information; INT, intervention; K10, Kessler Distress 10–Scale; No INT, did not receive intervention; Non-completers, participants who did not complete the assessment at that time point but continued with the study and were assessed at the following time point; P Nut MHL, placebo tablet, nutrition, mental health literacy; P Nut Pain, placebo tablet, nutrition, pain information; P PA MHL, placebo tablet, physical activity, mental health literacy; P PA Pain, placebo tablet, physical activity, pain information; RCT, randomized controlled trial.

participants in FA + vitamin B-12 and placebo groups who completed the 24-mo interview (chi-square$_1$ = 0.6, P = 0.420).

Oral FA + vitamin B-12 supplementation

In comparison with placebo, the FA + vitamin B-12 group showed a significant increase in concentrations of folate (an increase of 65.97% from 573 to 951 nmol/L; t_{690} = 12.0, $P < 0.001$; the placebo group had an increase of 1.97% from 557 to 568 nmol/L) and in vitamin B-12 (an increase of 55.74% from 305 to 475 nmol/L; t_{681} = 14.5, $P < 0.001$; the placebo group had an increase of 4.21% from 285 to 297 nmol/L) over the 24-mo period. Homocysteine increased significantly less in the FA + vitamin B-12 group (from 9.6 to 10.4 μmol/L; an increase of 8.33%) than in the placebo group (from 9.8 to 12.0; an increase of 22.45%; t_{649} = −5.6, $P < 0.001$).

Cognitive functioning

Variable estimates from the final models for the TICS-M total cognitive score, TICS-M immediate memory, and TICS-M delayed recall are presented in **Table 2**, with all of the models taking into account baseline homocysteine concentrations and depression levels. In addition to analyzing the data for the TICS-M total cognitive score, separate mixed-model repeated-measures ANOVAs were used for each TICS-M subscale to determine whether there were particular subscales that may further explain in which aspect of cognitive functioning any significant effect may have occurred. Findings for all other cognitive measures—ie, TICS-M orientation, TICS-M attention/calculation, TICS-M semantic memory, BTACT processing speed, and IQCODE informant-reported cognitive functioning—were not significant, and results are not shown.

Omnibus tests of time by intervention effects on TICS-M total scores were significant for FA + vitamin B-12 supplementation ($F_{2,788.4}$ = 5.26, P = 0.005). The FA + vitamin B-12 group had a significantly greater increase in TICS-M total scores from baseline to 24 mo than did the placebo group (P = 0.032, effect size = 0.17). The effect was not significant at 12 mo (P = 0.283). The FA + vitamin B-12 group showed significantly greater increases in performance than did the placebo control in TICS-M immediate recall (P = 0.046, effect size = 0.15) and TICS-M delayed recall (P = 0.013, effect size = 0.18) from baseline to 24-mo assessment (**Figure 2**).

In addition to the intervention effects, baseline homocysteine concentrations and depression scores had important associations with cognitive performance over time. Elevated homocysteine concentrations at baseline were associated with poorer cognitive performance at 24 mo for TICS-M overall cognitive performance (t_{835} = −2.93, P = 0.004), immediate recall (t_{893} = −4.95, P = 0.001), and delayed recall (t_{893} = −3.45, P = 0.001). Similarly, initially higher depression scores (Patient Health Questionnaire–9) were predictive of lower cognitive performance at 24 mo, including TICS-M overall cognitive score (t_{887} = −2.43, P = 0.016), immediate recall (t_{883} = −2.28, P = 0.023), and orientation (t_{861} = −2.27, P = 0.024).

Subsidiary analyses were conducted to determine the role of baseline homocysteine and change in homocysteine scores on cognitive functioning scores. The model was reevaluated with the inclusion of a measure of the overall change in homocysteine from baseline to 24 mo as a covariate (for completers of the 24-mo interview, n = 595). In this analysis, after baseline homocysteine concentrations were accounted for, smaller increases in homocysteine were associated with significantly larger increases in TICS-M total score from baseline to 12 mo (t_{605} = −2.01, P = 0.044), but there was no effect at 24 mo (t_{610} = −0.99, P = 0.325).

DISCUSSION

In this study, oral FA (400 μg/d) + vitamin B-12 (100 μg/d) supplementation led to significantly greater improvements in overall cognitive functioning scores (TICS-M total score) at 24 mo than did the placebo condition (effect size Cohen's d = 0.17, P = 0.032, with control for baseline covariates including depressive symptoms and concentrations of homocysteine, folate, and vitamin B-12). The FA + vitamin B-12 group had significantly greater improvements in both immediate (Cohen's d = 0.15, $P < 0.046$) and delayed (Cohen's d = 0.18, $P < 0.013$) recall from baseline to the completion of the intervention at 24 mo compared with the placebo group. No significant changes were evident for TICS-M orientation, attention/calculation, semantic memory, and BTACT processing speed informant-reported cognitive functioning.

Our findings are incongruent with some of the existing evidence that found no effect for FA and vitamin B-12 supplementation on cognitive performance (10, 13, 16, 39). Nonetheless, our study concurs with and extends previous evidence from both short- and long-term interventions (18, 40). For instance, one long-term intervention of 800 μg FA/d (36-mo duration) found benefits in memory and global function in healthy older adults with elevated plasma total homocysteine concentrations (40).

TABLE 1
Baseline characteristics for the FA + B_{12} and placebo intervention groups that comprise Australian older adults with elevated levels of distress[1]

Characteristics	Intervention: FA + vitamin B-12 (n = 447)	Intervention: Placebo (n = 453)	P value	Total (n = 900)
Age (y)	65.92 ± 4.30[2]	65.97 ± 4.18	0.861	65.94 ± 4.24
Men [n (%)]	181 (40.5)	177 (39.1)	0.664	358 (39.8)
Marital status [n (%)]				
Married/de facto	286 (64.0)	278 (61.4)	0.119	564 (6.72)
Separated/divorced	86 (19.2)	75 (16.6)		161 (17.2)
Widowed	51 (11.4)	59 (13.0)		110 (12.2)
Never married	24 (5.4)	41 (9.1)		65 (7.2)
Employment status [n (%)]				
Not in the labor force	270 (61.4)	289 (64.9)	0.117	569 (63.2)
Employed, full-time	72 (16.4)	50 (11.2)		130 (14.4)
Employed part-time	90 (20.5)	91 (20.4)		163 (18.1)
Unemployed	8 (1.8)	15 (3.4)		11 (1.2)
Education (y)	13.77 ± 2.71	13.92 ± 2.86	0.407	13.84 ± 2.78
Depression				
K10 score	17.28 ± 5.36	17.56 ± 5.15	0.430	17.42 ± 5.25
PHQ-9 depression score[3]	5.37 ± 4.21	5.58 ± 4.27	0.448	5.47 ± 4.24
0–9 [n (%)]	380 (85.0)	373 (82.5)		753 (83.8)
10–14 [n (%)]	48 (10.7)	59 (13.1)		107 (11.9)
15–19 [n (%)]	14 (3.1)	19 (4.2)		33 (3.7)
≥20 [n (%)]	5 (1.1)	1 (0.2)		6 (0.7)
No. of medical conditions	1.53 ± 1.19	1.48 ± 1.13	0.507	1.51 ± 1.16
Have vascular condition	0.71 ± 0.45	0.75 ± 0.43	0.162	0.73 ± 0.44
History of [n (%)]				
Brain tumor	3 (0.7)	4 (0.9)	0.718	7 (0.8)
Stroke	9 (2.0)	9 (2.0)	0.977	18 (2.0)
Mini-stroke	22 (4.9)	34 (7.5)	0.112	56 (6.2)
Serious head injury	47 (10.5)	55 (12.1)	0.420	102 (11.3)
Heart problem	79 (17.7)	85 (18.8)	0.683	164 (18.2)
Heart attack	13 (2.9)	15 (3.3)	0.810	28 (3.1)
Hypertension	206 (46.1)	231 (51.0)	0.140	437 (48.6)
Use of hypertension medication [n (%)]	172 (38.5)	196 (43.3)	0.939	368 (40.9)
Faintness/dizziness standing up [n (%)]	165 (36.9)	180 (39.7)	0.398	345 (38.3)
Cholesterol (mmol/L)	5.24 ± 0.99	5.23 ± 0.94	0.932	5.24 ± 0.96
Homocysteine in plasma (μmol/L)	9.59 ± 2.56	9.81 ± 2.78	0.215	9.70 ± 2.68
Red blood cell folate (nmol/L)	572.54 ± 266.32	557.09 ± 277.50	0.395	564.77 ± 271.96
Serum vitamin B-12 (nmol/L)	305.32 ± 151.05	285.27 ± 105.77	0.021[4]	295.24 ± 130.58
IPAQ MET (min/wk)	1705.99 ± 1791.81	1651.33 ± 1830.17	0.651	1678.45 ± 1810.44
Cognitive function				
BTACT processing speed	38.39 ± 10.64	37.95 ± 10.78	0.532	38.17 ± 10.71
IQCODE score	3.06 ± 0.25	3.03 ± 0.26	0.223	3.05 ± 0.26
TICS-M total score	26.42 ± 3.87	26.67 ± 3.69	0.316	26.55 ± 3.78
TICS-M orientation	6.65 ± 0.69	6.68 ± 0.62	0.415	6.66 ± 0.65
TICS-M immediate recall	5.16 ± 1.54	5.23 ± 1.59	0.500	5.19 ± 1.56
TICS-M delayed recall	3.75 ± 1.63	3.89 ± 1.63	0.203	3.82 ± 1.63

[1] Comparisons for each intervention arm were averaged over other arms. P values were based on F statistics for continuous variables and on chi-square statistics for categorical variables. Baseline data were collected from January to August 2006. BTACT, Brief Test of Adult Cognition by Telephone; FA, folic acid; IPAQ MET, International Physical Activity Questionnaire metabolic equivalent task; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; K10, Kessler Distress 10–Scale; PHQ-9, Patient Health Questionnaire–9; TICS-M, Telephone Interview of Cognitive Status–Modified.

[2] Mean ± SD (all such values).

[3] PHQ severity categories include the following: minimal-mild (0–9), moderate (10–14), moderately severe (15–19), and severe (≥20) (36).

[4] Those who received FA + vitamin B-12 had higher concentrations of serum vitamin B-12 than did those in the placebo group ($F_{1,898}$ = 5.33, P = 0.021).

Even though the findings for FA + vitamin B-12 supplementation were in keeping with some previous trials (18, 40), a number of our findings require explanation. First, the effect was evident for short- and long-term memory, but not processing speed, which may be explained by the relation between folate and hippocampal function. Evidence from RCTs (18, 40) and animal

TABLE 2
Mixed-model variables, significance, and CIs for TICS-M cognitive functioning scores in older adults with elevated distress in Australia[1]

Cognition score	Estimate SE[2]	*t*	*P* value	95% CI		Effect size, *d*
				Lower	Upper	
Total score						
Intercept	28.564 ± 0.673	42.45	0.001	27.24	29.88	
Folate (baseline)	−0.001 ± 0.001	−0.45	0.655	0.01	0.01	
Vitamin B-12 (baseline)	−0.001 ± 0.001	−0.92	0.356	0.01	0.01	
Homocysteine (baseline)	−0.127 ± 0.044	−2.93	0.004	−0.21	−0.04	
PHQ depression (baseline)	−0.065 ± 0.027	−2.43	0.016	−0.12	−0.01	
FA + vitamin B-12 intervention[3]	−0.290 ± 0.253	−1.15	0.251	−0.79	0.21	
Wave						
Baseline[4]	0.001 ± 0.001	.	.	.	.	
12 mo	0.804 ± 0.256	3.14	0.002	0.30	1.31	
24 mo	0.663 ± 0.274	2.42	0.016	0.13	1.20	
FA + vitamin B-12 × wave						
FA + vitamin B-12 × baseline[4]	0.001 ± 0.001	.	.	.	.	
FA + vitamin B-12 × 12 mo	−0.275 ± 0.256	−1.07	0.283	−0.78	0.23	0.076
FA + vitamin B-12 × 24 mo	0.585 ± 0.272	2.15	0.032	0.05	1.12	0.165[5,6]
Immediate recall score						
Intercept	6.234 ± 0.265	23.50	0.001	5.71	6.76	
Folate (baseline)	0.001 ± 0.001	−0.09	0.925	0.01	0.01	
Vitamin B-12 (baseline)	−0.001 ± 0.001	−0.48	0.629	0.01	0.01	
Homocysteine (baseline)	−0.084 ± 0.017	−4.95	0.000	−0.12	−0.05	
PHQ depression (baseline)	−0.024 ± 0.011	−2.28	0.023	−0.04	0.01	
Folate intervention[3]	−0.091 ± 0.104	−0.87	0.384	−0.29	0.11	
Wave						
Baseline[4]	0.001 ± 0.001	.	.	.	.	
12 mo	0.292 ± 0.119	2.46	0.014	0.06	0.53	
24 mo	0.258 ± 0.122	2.12	0.034	0.02	0.50	
FA + vitamin B-12 × wave						
FA + vitamin B-12 × baseline[4]	0.001 ± 0.001	.	.	.	.	
FA + vitamin B-12 × 12 mo	−0.064 ± 0.119	−0.54	0.592	−0.30	0.17	0.035
FA + vitamin B-12 × 24 mo	0.242 ± 0.121	2.00	0.046	0.01	0.48	0.149
Delayed recall score						
Intercept	4.726 ± 0.295	16.01	0.001	4.15	5.30	
Folate (baseline)	−0.001 ± 0.001	−0.72	0.469	0.01	0.01	
Vitamin B-12 (baseline)	−0.001 ± 0.001	−0.52	0.602	0.01	0.01	
Homocysteine (baseline)	−0.066 ± 0.019	−3.45	0.001	−0.10	−0.03	
PHQ depression (baseline)	−0.018 ± 0.012	−1.50	0.133	−0.04	0.01	
Folate intervention[3]	−0.156 ± 0.109	−1.43	0.153	−0.37	0.06	
Wave						
Baseline[4]	0.001 ± 0.001	.	.	.	.	
12 mo	0.404 ± 0.119	3.39	0.001	0.17	0.64	
24 mo	0.522 ± 0.125	4.18	0.001	0.28	0.77	
FA + vitamin B-12 × wave						
FA + vitamin B-12 × baseline[4]	0.001 ± 0.001	.	.	.	.	
FA + vitamin B-12 × 12 mo	0.027 ± 0.119	0.22	0.822	−0.21	0.26	0.006
FA + vitamin B-12 × 24 mo	0.308 ± 0.124	2.49	0.013	0.06	0.55	0.176

[1] *df* ranged from 773 to 1090. Data collection occurred from January 2006 to September 2008. FA, folic acid; PHQ, Patient Health Questionnaire; *t*, *t* test; TICS-M, Telephone Interview of Cognitive Status–Modified.

[2] Values are estimates + SEMs.

[3] Reference category was placebo.

[4] Reference category.

[5] Cohen's *d* refers to the magnitude of the standardized mean effect, ie, the mean difference between 2 groups in SD units. Significant at $P < 0.05$.

[6] Omnibus tests of time by intervention effects on TICS-M total scores were significant for FA + vitamin B-12 supplementation ($F_{2,788.4} = 5.26$, $P = 0.005$). The FA + vitamin B-12 group had a significantly greater increase in TICS-M total scores from baseline to 24 mo than did placebo ($P = 0.032$, effect size = 0.17). The FA + vitamin B-12 group showed significantly greater increases in performance than did the placebo control in TICS-M immediate recall ($P = 0.046$, effect size = 0.15) and TICS-M delayed recall ($P = 0.013$, effect size = 0.18) from baseline to the 24-mo assessment.

models (41) suggests that FA + vitamin B-12 supplementation may have a positive impact on global cognitive functioning and specifically on performance on memory tasks (42). In terms of memory performance, a proposed mechanism has been posited that a reduction in BDNF may be related to oxidative stress, which reduces BDNF mRNA expression, and in turn impairs the promotion of hippocampal neurons (43, 44). Elevated homocysteine concentrations may induce oxidative stress and related neurotoxicity,

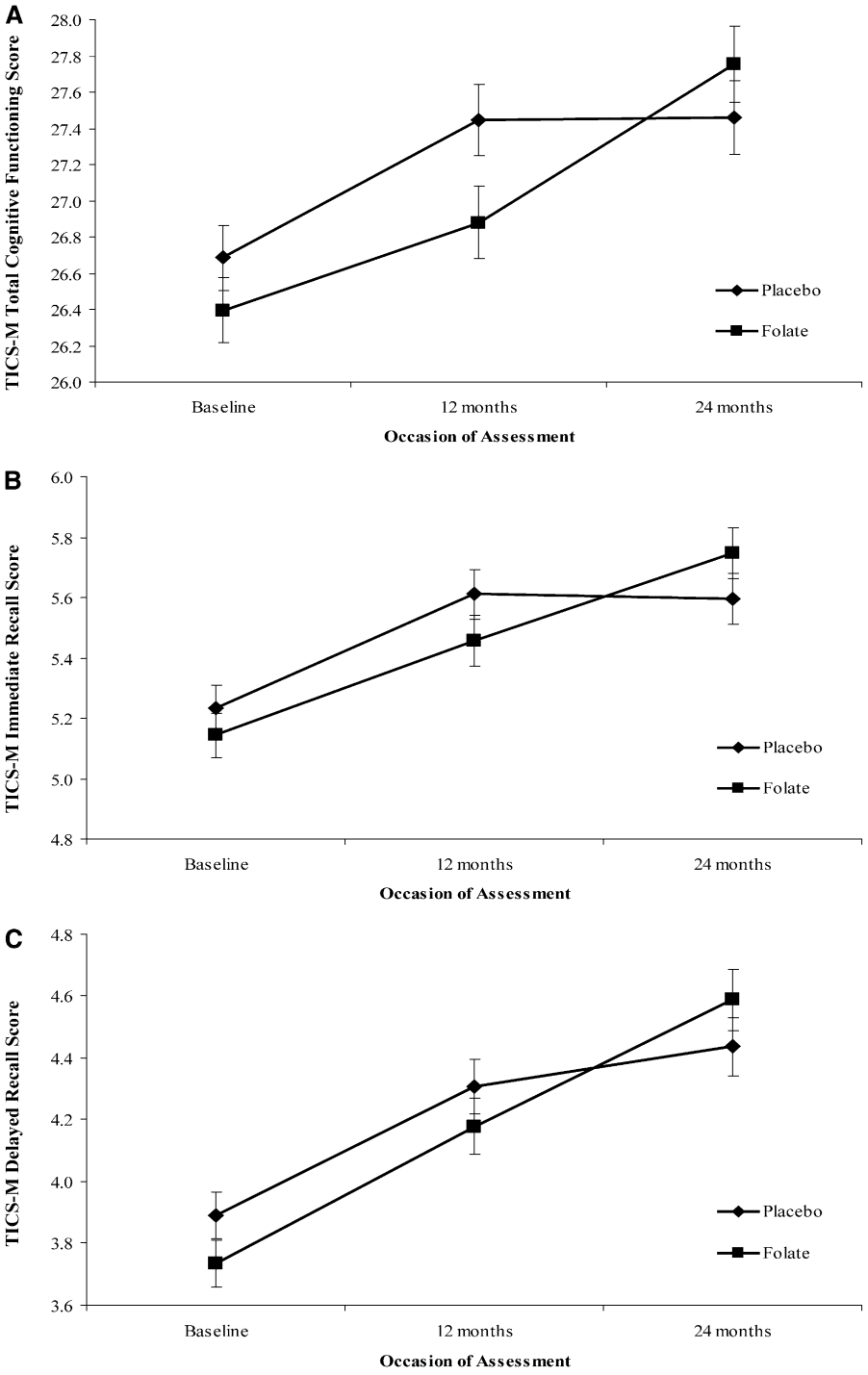

FIGURE 2. A–C: Mean (±SEM) population marginal means of TICS-M cognitive functioning scores by treatment group in community-dwelling older Australians (aged 60–74 y) with elevated distress symptoms. Folic acid intervention group, $n = 447$; placebo group, $n = 453$. Estimated population marginal means for the model are shown in Table 2. Folate, daily oral dose of 400 μg + 100 μg vitamin B-12 supplementation; TICS-M, Telephone Interview of Cognitive Status–Modified.

which possibly lead to reduced BDNF concentrations and impaired BDNF pathways in the hippocampus, that may impair memory consolidation (41, 44). These few possible mechanisms in the relation between folate concentrations and memory performance may explain our lack of effect found for processing speed. FA + vitamin B-12 supplementation may have greater effect on processes within the hippocampus and its functioning than on other processes or areas that are more connected to processing speed. Changes in processing speed may be associated with structural declines in neural networks in the prefrontal cortical and cerebella regions (45). In addition, processing speed involves the coordination of numerous activities (eg, perception, decision making) and processing speed tasks (45); hence, the complex interaction between numerous brain networks and processing speed as a construct may be too diffuse to benefit from changes related to FA + vitamin B-12 supplementation.

The significant effect of FA + vitamin B-12 supplementation occurred in the later stage of the intervention, ie, at 24 mo. It is possible that the effects of FA + vitamin B-12 supplementation are long term and operate by reducing vascular and other metabolic risk factors for cognitive impairment (10, 46). We found a modest association between larger increases in homocysteine concentrations and smaller increases in cognitive performance, suggesting that the effect is related to homocysteine concentrations. An alternative explanation, supported by evidence from animal models, is that folate deficiency and elevated homocysteine concentrations impair DNA repair in hippocampal neurons and sensitize them to amyloidal toxicity (47). The latter mechanism may be plausible because a recent study showed a higher retention of Pittsburgh Compound-B, a selective imaging ligand for β-amyloid in the brain, in depressive patients compared with controls (48). Furthermore, folate and vitamin B-12 may selectively benefit the hippocampus, because this is one of the unique regions in the brain in which cell renewal and DNA replication occurs and therefore may have a higher dependence on these vitamins that are essential for nucleotide synthesis (49). Despite the lack of clarity regarding the mechanism of FA + vitamin B-12 supplementation in cognitive performance and decline, we found that 400 μg FA + 100 μg vitamin B-12/d is potentially an effective long-term intervention for minimizing cognitive decline in a dose that can be recommended as a dietary supplement.

Finally, the overall cognitive functioning scores (Cohen's $d = 0.31$, $P < 0.001$), as well as immediate ($P = 0.034$) and delayed ($P < 0.001$) recall, improved over the 2-y period. This was likely due to practice effects. The fact that greater improvement in performance occurred with FA + vitamin B-12 supplementation is consistent with suggestions that those with a capacity to learn may be less prone to experience cognitive decline (50).

Strengths and limitations

In interpreting the benefits found in public health terms, it is important to bear in mind that we received 23.19% of surveys originally sent out into the community, and only 3.7% of those who returned their surveys met the selection criteria to participate in the intervention, which may create uncertainty about generalizing from our findings. This relatively small group in comparison to the total of surveys returned was a consequence of ethical and institutional requirements. In addition, by virtue of the primary aims of the study, our entire sample had moderate to high levels of distress compared with population studies, which indicates that the majority (74.5%) of older adults aged 65–74 y experience low levels of distress (51). Subsequently, the present findings may differ from other cognition studies without this risk.

It is also important to acknowledge that the positive effect of FA + vitamin B-12 supplementation on overall cognitive performance at 24 mo was small (Cohen's $d = 0.17$, $P = 0.032$). This finding was of modest clinical significance at the level of the individual; however, an improvement in cognitive function of this magnitude at a community level could lead to large national health benefits and significant cost savings (10). Moreover, because the sample was relatively young, the effect might be more significant because cognitive deterioration accelerates at older ages. This would need to be tested.

This is one of the largest trials to date to examine the effectiveness of dietary supplementations in preventing cognitive decline in community-dwelling older adults.

Conclusions and further research

Our findings suggest that there may be a role for combined FA + vitamin B-12 in lowering the risk of cognitive decline. Such an intervention is inexpensive, and at the population level the preventive effect may be considerable (10), at least among people with subsyndromal depressive disorders. The prospect of using dietary supplements of FA and vitamin B-12 to prevent cognitive decline appears promising. More studies are needed to determine whether the benefits of FA and vitamin B-12 supplementation found in this trial could be replicated in other populations of older adults with increased risk of developing significant cognitive impairment.

We thank the participants of the Beyond Ageing Project for their involvement and enthusiasm. We gratefully acknowledge the support of Elizabeth Parkes and the telephone interviewing team; the research assistance from Amanda George; and the administrative support from Carmel Poyser, Kim Pullen, Trish Jacomb, and Karen Maxwell; and input in the research conception and design from Kaarin Anstey, Mike Bird, and Kathy Griffiths.

The authors' responsibilities were as follows—AFJ, IH, HC, and JGW: designed the study; JGW, DC, and HC: acquired the data; PJB and AJM: analyzed the data; JGW, HC, PJB, AJM, AFJ, and DC: drafted the manuscript; HC, JGW, AJM, PJB, AFJ, IH, MF, and MK: provided critical revision of the manuscript for important intellectual content; AFJ, HC, and IH: obtained funding; and JGW and HC: supervised the study. All authors had access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analyses and final report. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. None of the authors had any conflicts of interest.

REFERENCES

1. Busse A, Bischkopf J, Riedel-Heller S, Angermeyer M. Mild cognitive impairment: prevalence and incidence according to different diagnostic criteria. Br J Psychiatry 2003;182:449–54.
2. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, et al. Prevalence of cognitive impairment without dementia in the United States. Ann Intern Med 2008;148:427–34.
3. Jagger C, Matthews R, Lindesay J, Robinson T, Croft P, Brayne C. The effect of dementia trends and treatments on longevity and disability: a simulation model based on the MRC Cognitive Function and Ageing Study (MRC CFAS). Age Ageing 2009;38:319–25.
4. Artero S, Touchon J, Ritchie K. Disability and mild cognitive impairment: a longitudinal population-based study. Int J Geriatr Psychiatry 2001;16:1092–7.
5. Daly E, Zaitchik D, Copeland M, Schmahmann J, Gunther J, Albert M. Predicting conversion to alzheimer disease using standardized clinical information. Arch Neurol 2000;57:675–80.
6. Mohajeri MH, Leuba G. Prevention of age-associated dementia. Brain Res Bull 2009;80:315–25.
7. Shineman DW, Fillit H. Novel strategies for the prevention of dementia from alzheimer's disease. Dialogues Clin Neurosci 2009;11:129–34.
8. Dufouil C, Alperovitch A, Ducros V, Tzourio C. Homocysteine, white matter hyperintensities, and cognition in healthy elderly people. Ann Neurol 2003;53:214–21.
9. Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PWF, Wolf PA. Plasma homocysteine as a risk factor for dementia and alzheimer's disease. N Engl J Med 2002;346:476–83.
10. Balk EM, Raman G, Tatsioni A, Chung M, Lau J, Rosenberg I. Vitamin B_6, B_{12} and folic acid supplementation and cognitive function: a systematic review of randomized trials. Arch Intern Med 2007;167:21–30.

11. Eussen SJ, de Groot LC, Joosten LW, Bloo RJ, Clarke R, Ueland PM, Schneede J, Blom HJ, Hoefnagels WH, van Staveren WA. Effect of oral vitamin B_{12} with or without folic acid on cognitive function in older people with mild vitamin B_{12} deficiency: a randomized, placebo-controlled trial. Am J Clin Nutr 2006;84:361–70.
12. Hvas AM, Juul S, Lauritzen L, Nexø E, Ellegaard J. No effect of vitamin B_{12} treatment on cognitive function and depression: a randomized placebo controlled study. J Affect Disord 2004;81:269–73.
13. Stott DJ, MacIntosh G, Lowe GDO, Rumley A, McMahon AD, Langhorne P, Tait RC, O'Reilly DSJ, Spilg EG, MacDonald JB, et al. Randomized controlled trial of homocysteine-lowering vitamin treatment in elderly patients with vascular disease. Am J Clin Nutr 2005; 82:1320–6.
14. Lewerin C, Matousek M, Steen G, Johansson B, Steen B, Nilsson-Ehle H. Significant correlations of plasma homocysteine and serum methylmalonic acid with movement and cognitive performance in elderly subjects but no improvement from short-term vitamin therapy: a placebo-controlled randomized study. Am J Clin Nutr 2005;81:1155–62.
15. Sun Y, Lu C-J, Chien K-L, Chen S-T, Chen R-C. Efficacy of multivitamin supplementation containing vitamins B_6 and B_{12} and folic acid as adjunctive treatment with a cholinesterase inhibitor in alzheimer's disease: a 26-week, randomized, double-blind, placebo-controlled study in taiwanese patients. Clin Ther 2007;29:2204–14.
16. Aisen PS, Schneider L, Sano M, Diaz-Arrastia R, van Dyck CH, Weiner MF, Bottiglieri T, Jin SM, Stokes KT, Thomas RG, et al. High-dose B vitamin supplementation and cognitive decline in alzheimer disease: a randomized controlled trial. JAMA 2008;300:1774–83.
17. van Uffelen JGZ, Chinapaw MJM, van Mechelen W, Hopman-Rock M. Walking or vitamin B for cognition in older adults with mild cognitive impairment? a randomised controlled trial. Br J Sports Med 2008;42: 344–51.
18. Fioravanti M, Ferrario E, Massaia M, Cappa G, Rivolta G, Grossi E, Buckley AE. Low folate levels in the cognitive decline of elderly patients and the efficacy of folate as a treatment for improving memory deficits. Arch Gerontol Geriatr 1998;26:1–13.
19. Reynolds EH. Folic acid, ageing, depression, and dementia. BMJ 2002; 324:1512–5.
20. Walker JG, Mackinnon A, Batterham P, Jorm A, Hickie I, McCarthy A, Fenech M, Christensen H. Mental health literacy, folic acid and vitamin B12, and physical activity for the prevention of depression in older adults: a randomised controlled trial. Br J Psychiatry 2010;197: 45–54.
21. Naismith SL, Hickie IB, Turner K, Little CL, Winter V, Ward PB, Wilhelm K, Mitchell P, Parker G. Neuropsychological performance in patients with depression is associated with clinical, etiological and genetic risk factors. J Clin Exp Neuropsychol 2003;25:866–77.
22. Barnes DE, Alexopoulos GS, Lopez OL, Williamson JD, Yaffe K. Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. [see comment] Arch Gen Psychiatry 2006;63:273–9.
23. Duff K, Beglinger LJ, Moser DJ, Paulsen JS, Schultz SK, Arndt S. Predicting cognitive change in older adults: the relative contribution of practice effects. Arch Clin Neuropsychol 2010;25:81–8.
24. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, Walters EE, Zaslavsky AM. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med 2002;32:959–76.
25. Andrews G, Slade T. Interpreting scores on the Kessler Psychological Distress Scale (K10). Aust N Z J Public Health 2001;25:494–7.
26. Cole BF, Baron J, Sandler R, Haile R, Ahnen D, Bresalier R, McKeown-Eyssen G, Summers R, Rothstein R, Burke C, et al. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA 2007;297:2351–9.
27. Social Psychiatry Research Unit. The Canberra Interview for the Elderly (CIE): a new field instrument for the diagnosis of dementia and depression by ICD-10 and DSMIII-R. Acta Psychiatr Scand 1992;85: 105–13.
28. Kessler RC, Barker P, Colpe LJ, Epstein JF, Gfroerer JC, Hiripi E, Howes MJ, Normand SL, Manderscheid RW, Walters EE, et al. Screening for serious mental illness in the general population. Arch Gen Psychiatry 2003;60:184–9.
29. de Jager CA, Budge M, Clarke R. Utility of TICS-M for the assessment of cognitive function in older adults. Int J Geriatr Psychiatry 2003;18: 318–24.
30. Cook SE, Marsiske M, McCoy KJM. The use of the Modified Telephone Interview for Cognitive Status (TICS-M) in the detection of amnestic mild cognitive impairment. J Geriatr Psychiatry Neurol 2009; 22:103–9.
31. Tun PA, Lachman ME. Telephone assessment of cognitive function in adulthood: the Brief Test of Adult Cognition by Telephone. Age Ageing 2006;35:629–32.
32. Herzog AR, Wallace RB. Measures of Cognitive Functioning in the AHEAD Study. J Gerontol B Psychol Sci Soc Sci 1997;52:37–48.
33. Weuve J, Kang JH, Manson JE, Breteler MMB, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. JAMA 2004;292:1454–61.
34. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. Psychol Med 1994;24:145–53.
35. Jorm AF. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): a review. Int Psychogeriatr 2004;16:275–93.
36. Kroenke K, Spitzer R, Williams J. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–13.
37. Schulz KF, Grimes D. Multiplicity in randomised trials: endpoints and treatments. Lancet 2005;365:1591–5.
38. Steel RGD, Torrie JH. Principles and procedures of statistics. 2nd ed. New York, NY: McGraw-Hill Book Company, 1980.
39. Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database Sys Rev 2008;4:CD004514.
40. Durga J, van Boxtel MPJ, Schouten EG, Kok FJ, Jolles J, Katan MB, Verhoef P. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet 2007;369:208–16.
41. Matté C, Pereira LO, Dos Santos TM, Mackedanz V, Cunha AA, Netto CA, Wyse ATS. Acute homocysteine administration impairs memory consolidation on inhibitory avoidance task and decreases hippocampal brain-derived neurotrophic factor immunocontent: prevention by folic acid treatment. Neuroscience 2009;163:1039–45.
42. Streck EL, Vieira PS, Wannmacher CMD, Dutra-Filho CS, Wajner M, Wyse ATS. In vitro effect of homocysteine on some parameters of oxidative stress in rat hippocampus. Metab Brain Dis 2003;18:147–54.
43. Dias VV, Brissos S, Frey B, Andreazza A, Cardoso C, Kapczinski F. Cognitive function and serum levels of brain-derived neurotrophic factor in patients with bipolar disorder. Bipolar Disord 2009;11:663–71.
44. Ho PI, Ashline D, Dhitavat S, Ortiz D, Collins SC, Shea TB, Rogers E. Folate deprivation induces neurodegeneration: roles of oxidative stress and increased homocysteine. Neurobiol Dis 2003;14:32–42.
45. Eckert MA, Keren NI, Roberts DR, Calhoun VD, Harris KC. Age-related changes in processing speed: unique contributions of cerebellar and prefrontal cortex. Front Hum Neurosci 2010;4:1–14.
46. de Lau LML, Refsum H, Smith AD, Johnston C, Breteler MMB. Plasma folate concentration and cognitive performance: Rotterdam Scan Study. Am J Clin Nutr 2007;86:728–34.
47. Kruman II, Kumaravel TS, Lohani A, Pedersen WA, Cutler RG, Kruman Y, Haughey N, Lee J, Evans M, Mattson MP. Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer's disease. J Neurosci 2002;22:1752–62.
48. Butters MA, Klunk W, Mathis C, Price J, Ziolko S, Hoge J, Tsopelas N, Lopresti B, Reynolds CR, DeKosky S, et al. Imaging Alzheimer pathology in late-life depression with PET and Pittsburgh Compound-B. Alzheimer Dis Assoc Disord 2008;22:261–8.
49. Fenech M. Folate, DNA damage and the aging brain. Mech Ageing Dev 2010;131:236–41.
50. Duff K, Beglinger L, Schultz S, Moser D, McCaffrey R, Haase R, Westervelt H, Langbehn D, Paulsen J; Huntington's Study Group. Practice effects in the prediction of long-term cognitive outcome in three patient samples: a novel prognostic index. Arch Clin Neuropsychol 2007;22:15–24.
51. Australian Bureau of Statistics. Information paper: use of the Kessler Psychological Distress Scale in ABS Health Surveys, Australia, 2001. Canberra, Australia: Australian Bureau of Statistics, 2003.

Update

The American Journal of Clinical Nutrition
Volume 96, Issue 2, August 2012, Page 448

DOI: https://doi.org/10.3945/ajcn.112.042804

three groups of American Indians: the Strong Heart Dietary Study, phase II. J Am Diet Assoc 2005;105:1895–903.
4. Teufel NI. Development of culturally competent food-frequency questionnaires. Am J Clin Nutr 1997;65:1173S–8S.
5. Serdula M, Byers T, Coates R, Mokdad A, Simoes EJ, Eldridge L. Assessing consumption of high-fat foods: the effect of grouping foods into single questions. Epidemiology 1992;3:503–8.
6. Willett W. Nutritional epidemiology. New York, NY: Oxford University Press, 1998.
7. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392–404.
8. Vergnaud AC, Norat T, Romaguera D, Mouw T, May AM, Travier N, Luan J, Wareham N, Slimani N, Rinaldi S, et al. Meat consumption and prospective weight change in participants of the EPIC-PANACEA study. Am J Clin Nutr 2010;92:398–407.

doi: 10.3945/ajcn.112.041038.

Erratum

Hall KD, Heymsfield SB, Kemnitz JW, Klein S, Schoeller DA, Speakman JR. Energy balance and its components: implications for body weight regulation. Am J Clin Nutr 2012;95:989–94.

An error appears in the print version of this article. In the fourth sentence of the first paragraph, the American College of Sports Medicine was inadvertently listed as a partner organization that helped convene the panel that developed the consensus statement on energy balance. The sentence should instead read as follows: ''Therefore, the ASN and the International Life Sciences Institute convened a panel composed of members with expertise in weight management, energy metabolism, physical activity, and behavior to review the published scientific literature and to hear presentations from other experts in these fields.''

doi: 10.3945/ajcn.112.042788.

Erratum

Walker JG, Batterham PJ, Mackinnon AJ, Jorm AF, Hickie I, Fenech M, Kljakovic M, Crisp D, Christensen H. Oral folic acid and vitamin B-12 supplementation to prevent cognitive decline in community-dwelling older adults with depressive symptoms—the Beyond Ageing Project: a randomized controlled trial. Am J Clin Nutr 2012;95:194–203.

The units for serum vitamin B-12 in the ''Oral FA + vitamin B-12 supplementation'' section on page 198 and in Table 1 on page 199 should be pmol/L instead of nmol/L.

doi: 10.3945/ajcn.112.042804.

Erratum

Heo M, Faith MS, Pietrobelli A, Heymsfield SB. Percentage of body fat cutoffs by sex, age, and race-ethnicity in the US adult population from NHANES 1999–2004. Am J Clin Nutr 2012;95:594–602.

On page 595, 2 of the race-ethnicity labels in the first column of Table 1 were switched. The ''MEX'' and ''NHB'' labels should be reversed. In Table 2 on page 596, the sample size (*n*) for NHW men should be 3347 instead of 3374.

doi: 10.3945/ajcn.112.042812.