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Research Article

A High Omega-3 Fatty Acid Multinutrient Supplement Benefits Cognition and Mobility in Older Women: A Randomized, Double-blind, Placebo-controlled Pilot Study

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Abstract

Background. Mobility is a key determinant of frailty in older persons, and a variety of dietary factors, such as the omega-3 fatty acid docosahexaenoic acid (DHA), are positively associated with decreased frailty and improved mobility and cognition in older persons.
Methods. The effects of a multinutrient supplement on mobility and cognition were assessed in postmenopausal women (60–84 years). Participants received either Efalex Active 50+ (1 g DHA, 160 mg eicosapentaenoic acid, 240 mg *Ginkgo biloba*, 60 mg phosphatidylserine, 20 mg d-α tocopherol, 1 mg folic acid, and 20 µg vitamin B12 per day; $N = 15$) or placebo ($N = 12$) for 6 months. Mobility was assessed by VICON 9 motion capture camera system synchronized with Kistler force plates, cognitive performance by computerized cognitive function tests, and blood fatty acid levels by pin-prick analysis.
Results. Significant effects of treatment were seen in two of the four cognitive tests, with shorter mean latencies in a motor screening task ($p < .05$) and more words remembered ($p < .03$), and one of the three primary mobility measures with improved habitual walking speed ($p < .05$). Compared with the placebo group, supplementation also resulted in significantly higher blood DHA levels ($p < .02$).
Conclusions. In this pilot study, multinutrient supplementation improved cognition and mobility in able older females at clinically relevant levels, suggesting a potential role in reducing the decline to frailty.

Key words: Aging—B vitamins—Gait—Memory—Docosahexaenoic acid

There is a complex relationship between cognition and mobility, whereby a decline in gait performance coexists with or precedes onset of cognitive decline in older persons (1). Interventions targeting cognition improve mobility (1) and improvements in mobility predict reduced mortality (2). Given the increased social and economic burden of a frail aging population, it is important to identify lifestyle interventions able to preserve mobility and cognition. A number of dietary factors may represent such interventions including omega-3 polyunsaturated fatty acids (PUFAs), vitamin E, phosphatidylserine, B vitamins, and *Ginkgo biloba*.

The omega-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) may confer benefits in neurodegenerative conditions (3) and mobility in older persons (4). Elevated levels of vitamin E (α-tocopherol) are associated with reduced risk of cognitive impairment in older persons (5); however, clinical trials have failed to demonstrate benefits (6). This dissonance may be due to the predominant role of α-tocopherol being supportive, protecting PUFAs, particularly DHA, in membranes (7). PS supplementation may benefit cognition in the elderly populations (8). Membrane DHA is a positive modulator of PS biosynthesis, and it is unclear whether the beneficial effects of PS are due to intact PS or DHA released following hydrolysis (9). Elevated plasma homocysteine is a risk factor for brain atrophy and cognitive decline, and treatment with B vitamins reduces brain

atrophy and may slow cognitive decline (10). Interestingly, recent evidence suggests an important interaction between B vitamins and DHA in the cognitively impaired elderly populations (11). *Ginkgo biloba* is a widely studied herbal extract for cognitive impairment, and although evidence of clinical benefits is inconsistent, a recent meta-analysis indicates it may slow cognitive decline (12).

A recent review highlights the importance of taking a more holistic approach to research into nutrition and brain aging, exploring potential synergies between nutrients as found in a balanced diet (13). Taking this approach, the main objective was to identify whether a commercially available preparation containing a range of dietary factors indicated to improve cognition (DHA, EPA, *Ginkgo biloba*, PS, α-tocopherol, folic acid and vitamin B12) improves cognition and mobility in able older females. Preliminary in vitro evidence in our laboratory suggests that this specific combination of nutrients may have synergistic neuroprotective and anti-inflammatory properties (M. Sakthithasan, PhD, R.E. Ward, PhD, Michael-Titus, Doct en Sci, P. Clough, MSc, unpublished data, 2008). Secondary objectives were to explore the nature of the relationship between DHA levels and these outcomes, since DHA is a major unifying factor in the effects of many of these nutrients.

Methods

See Supplementary Material for detailed methodology.

Participants

A stratified block randomization design matching the number of nonfrail, prefrail, and frail participants between groups was used. Randomization was performed using an online sample generator and frailty classified by phenotype (14). All analyses were conducted at the University of Roehampton, London, UK, which granted ethical approval. All participants provided written informed consent. All outcome measures were collected at baseline and 6 months by a research assistant, who along with the participants was blinded to the intervention groups.

Nonacutely ill females aged 60 and older were recruited and screened by the following criteria: community dwelling, able to walk at least 50 m, and negotiate stairs independently. Exclusion criteria were vestibular impairments, neurological disorder, lower limb surgery, allergy to seafood, or regular consumption of multivitamin/fish oil supplements. Subjects were recruited by invitation from existing databases, and community presentations to senior centers and community groups.

Intervention

Participants received four capsules per day of Efalex Active 50+ (N = 15) or placebo (N = 12) throughout the 24-week study. The intervention provided 1 g DHA and 160 mg EPA per day in addition to *Ginkgo biloba*, PS, α-tocopherol, folic acid, and vitamin B12 (See Supplementary Table S1). The control group received capsules containing an isocalorific oil blend matched to the composition of the typical fat content of an average diet. Participants were told to take their daily supply of capsules with their largest meal of the day. The capsules were counted, coded, and allocated by the principal investigator, who was not involved in the assessment. Compliance was measured by changes in DHA levels compared to baseline, counting returned pills at the midpoint and end of the study, and exit questionnaire. Adverse events were monitored by subject self-reporting and exit questionnaire.

Outcome Measures

The primary outcome measures were based on changes in mobility and cognition. Habitual walking (HW) speed is a sensitive measure of overall health and function and recommended as a primary outcome in interventions on elderly populations (15). In older people, faster habitual and maximal gait speed predicts increased longevity (16). Therefore, both HW and fast walking (FW) speed were included as primary outcomes. Vertical jump height (VJH) has been studied to assess the body's ability to rapidly produce force in a coordinated manner (17) and was also included as a primary mobility outcome. The importance of information processing speed (18) and executive function (19) in gait has consistently been shown; however, associations with memory decline have also been identified (19). Therefore, psychomotor response latency (MOT) as an index of information processing speed, executive function, Verbal Recognition Memory (VRM), and paired associate learning (PAL) were primary cognitive outcomes.

In order to identify potential mechanisms behind improvements in gait speed, cadence and stride length were included as secondary outcomes. The relationship between blood DHA status (DHA levels and ratio of the omega-6 fatty acid, arachidonic acid [AA] to DHA [AA:DHA]) and cognitive and mobility outcomes at baseline and at the end of the study were also included as further secondary outcomes.

Mobility

HW and FW speed, cadence and step length and VJH were analyzed using a nine camera VICON system integrated with two Kistler force plates. The mean of five trials was taken for gait, whereas the best of three maximal jumps was analyzed for VJH. Speed, cadence, and step length were calculated using Nexus software (Version 1.8.5, Oxford Metrics Group, UK). VJH was calculated as the height (mm) of the pelvis during static standing subtracted from the highest vertical displacement during flight.

Cognition

A battery of computer-based cognitive tests (CANTAB, Cambridge Cognition Ltd.) was performed. Psychomotor response latency 'motor screening task' (MOT), two memory tests (VRM) and (PAL), and one executive function test (Stockings of Cambridge) were analyzed.

Blood Fatty Acid Analysis

Fingertip pin-prick blood samples were collected to analyze fatty acid composition using a previously validated method on nonfasted subjects (20). Individual fatty acids were identified by gas chromatography coupled with flame ionization detector (Agilent technologies, USA), as described previously (21).

Statistical Analysis

Results are reported according to the CONSORT statement (22). Groups were compared at baseline by student's t test for two independent samples or Freeman-Halton extension of the Fisher exact probability test. Associations between cognition, mobility, and DHA status were examined using Pearson's partial correlations, controlling for age. National Adult Reading Test score was also included as a covariate in preliminary analysis, but as it did not influence results, it was excluded in final models. DHA levels and mobility were further explored at baseline by multiple regression, with DHA the predictor variable and age, body mass index, physical activity,

and grip strength included. Correlation and regression data were examined to ensure assumptions were not violated. For the regression analyses, a sample size of 29 was required to achieve a power of 0.80 for a correlation coefficient of 0.50 and an α of 0.05, for a two-tailed test (23).

Treatment effects were analyzed by general linear model and analysis of variance on cognition and mobility from the final session with baseline data and age as covariates and were calculated based on differences between the treatment groups adjusted mean values. Due to the preliminary nature of the study, sample size was determined based on HW speed, where meaningful differences of between 0.05 and 0.08 m/s have been suggested (24,25). The sample size calculation was therefore based on a difference of 0.07 m/s with a power of 0.8 and an α of 0.05 (one-tailed test). A minimum sample size of 17 participants per group was required to detect an effect size *d* of 0.8 (G*Power 3.1.10) (26). In all analyses, $p < .05$ was considered significant, and there was no multiple-test adjustment of *p* values to avoid Type-II errors, as recommended (27). One-tailed *p* values are given where the direction was predicted by the hypotheses, otherwise two-tailed values are given. Statistical analyses were performed using IBM SPSS statistics version 21 (Chicago, Illinois). All results are expressed as means (*SD*).

Results

Participants

Participant flow is shown in Figure 1. In total, 12/14 of the placebo group and 15/15 of the intervention group completed the study. One subject moved prior to allocation and another was diagnosed with a medical condition excluding them from analysis. Analyses were conducted on those who completed the study with no exclusions irrespective of compliance or protocol violations. For baseline characteristics, see Supplementary Table S2. There were no reported side effects in either group during the study. Compliance measured by changes in blood DHA levels was 66.7% in both groups, whereas compliance measured by capsule counts was higher and also not significantly different between groups (placebo, 86.1% [12.3%] and intervention, 89.8% [15.1%]). None of the participants reported changing their physical activity or diet during the study.

Primary Outcome Measures

Effects of treatment on cognition and mobility

The significant effects of 6 months mixed multinutrient supplementation versus placebo on cognition and mobility are summarized in Table 1. The intervention resulted in significantly shorter MOT mean latencies to touch compared with placebo [$F(1,23) = 3.47$, $p = .038$, one-tailed], with a mean adjusted difference between groups of 118 ms and medium effect size ($\eta_p^2 = 0.13$). There were no significant effects on MOT mean errors (touch accuracy). In the VRM test, the intervention resulted in significantly more words immediately remembered compared with placebo [$F(1,23) = 4.00$, $p = .029$, one-tailed], with a mean adjusted difference of 1.3 words out of a maximum of 12 and medium effect size ($\eta_p^2 = 0.15$). The intervention had no effects on the total number of words recognized after 20 min delay or on PAL or Stockings of Cambridge tests. The intervention resulted in a significant improvement in HW speed compared to placebo [$F(1,23) = 3.88$, $p = .031$, one-tailed], with mean adjusted difference of 0.07 m/s and medium effect size ($\eta_p^2 = 0.14$). There were no significant treatment effects on FW speed or VJH.

Secondary Outcome Measures

Effects of treatment on gait parameters

There were no significant effects of treatment on cadence or stride length for HW or FW, summarized in Table 2.

Fatty acid analysis

At baseline, age was significantly associated with lower levels of total omega-3 PUFAs, (Pearson correlation –0.431, $p = .025$), EPA (–0.462, $p = .015$), and DHA (–0.436, $p = .023$). Therefore, age was included as a covariate in all analyses. There were no significant differences between groups at baseline for any fatty acid. Following supplementation, the intervention group showed significant increases in DHA of 17% [$F(1,23) = 6.52$, $p = .018$] and EPA of 71% [$F(1,23) = 11.66$, $p < .002$] and decreases in AA of 18% [$F(1,23) = 6.99$, $p < .015$] compared with the placebo group, adjusted for age and baseline values. There were no significant effects of treatment on AA:DHA or other fatty acids.

Baseline correlations

Partial correlations (Table 3) identified significant associations between DHA levels and all measures of mobility, and AA:DHA was significantly associated with both HW and FW speeds. There were also trends for associations between DHA and AA:DHA and grip strength, $p < .062$ and $p < .067$, respectively. There were no significant correlations between DHA or AA:DHA and cognition, or between cognition and mobility. All mobility outcomes were highly correlated with each other, whereas there were no significant correlations between cognitive tests.

When the predictor variables were modeled together by multiple regression for HW speed, there were no significant effects of body mass index, age, or grip strength. DHA and Physical Activity Scale of the Elderly remained significant following adjustments, explaining 47% of the variance (adjusted $R^2 = .469$; Table 4). Similarly, for FW speed, DHA and Physical Activity Scale of the Elderly also remained significant, explaining 41% of the variance (Adjusted $R^2 = .412$). With VJH there were significant effects of age, DHA and body mass index after adjustments, explaining 65% of the variance (Adjusted $R^2 = .646$).

The relationships between changes in DHA status and changes in cognition and mobility at the end of the study were investigated and are shown in the Supplementary Material and Supplementary Table 3.

Discussion

This pilot study shows for the first time that a multinutrient supplement significantly improves some measures of cognition and mobility in able older females. There were significant improvements in the two of the four cognitive tests (MOT and VRM) and one of the three primary mobility measures (HW speed), all with medium effect sizes. Furthermore, lower circulating DHA was associated with poorer mobility, and increasing DHA was positively associated with improvements in walking speeds. However, due to the lack of statistical power, these observations can only be considered preliminary.

The improvements in verbal memory are consistent with previous reports of positive effects with DHA (900 mg/d) on VRM (28).

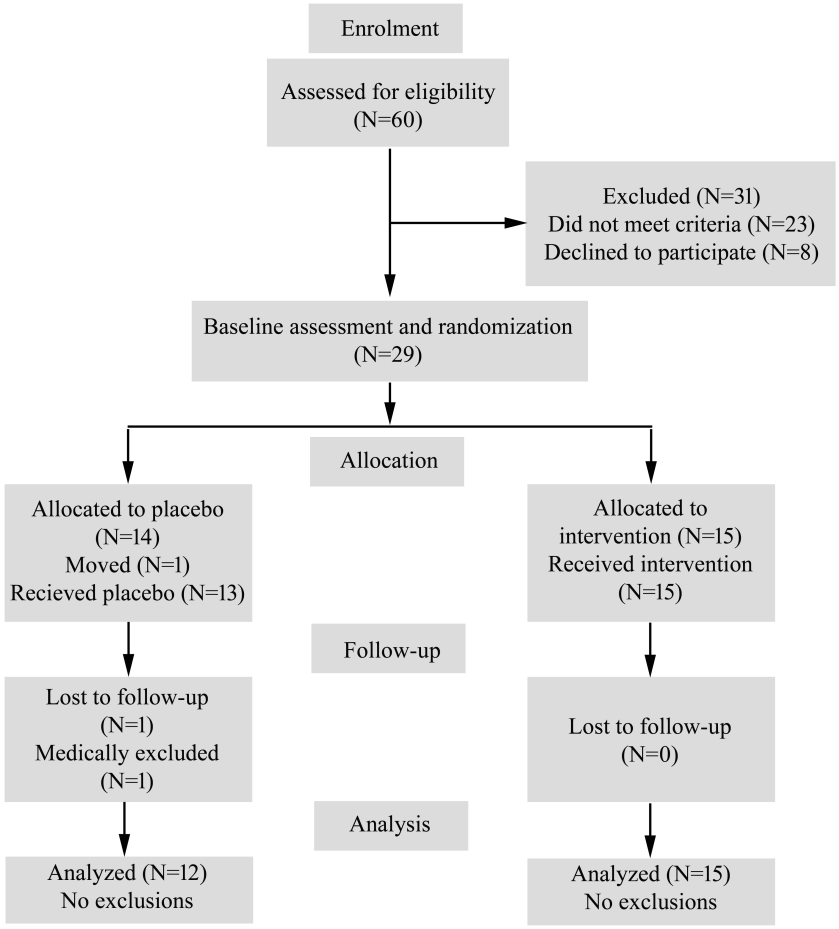

Figure 1. CONSORT diagram reflecting flow of study participants through the study.

However, this group reported improvements with immediate and delayed word recognition, rather than free recall. They also found significant improvements in the PAL memory test (six pattern errors). The differences may be due to different abilities between the study participants. In their study, the participants performed at much lower levels, and our participants may have suffered from ceiling effects, for example, our participants recognized 11.5 of 12 target words on average. Indeed, a mean of 9.0 words for immediate recall is more consistent with a much younger age range (29).

Improvements in psychomotor response latency (MOT) were also seen following treatment. Previous studies with either omega-3 PUFAs (30) or folic acid and vitamin B12 (31) supplementation have failed to provide evidence of beneficial effects on information processing speed in older adults. However, beneficial effects have been reported in younger adults (32), and it may be that the synergistic combination of nutrients found in the multinutrient supplement has a greater effect than individual nutrients in older persons.

The treatment significantly improved HW speed. Maintaining walking speed in old age is clinically important as speed is a risk factor for cognitive impairment, falls, and mortality (15). Our participants were extremely fit at baseline (15), but significant improvements were still seen. The difference in adjusted mean scores represented a 0.07 m/s improvement between groups, reflecting clinically relevant improvements (25). Contributing to the effects were decreases in the average speed of the placebo group slightly greater than would be predicted (33) and improvements in the intervention group. There was no single factor driving the improvements as there were trends for improvements in both stride length and cadence.

No significant effects were observed with FW speed or VJH. The placebo group maintained their FW speed over the study, contrary to expectations (34), which may have mitigated treatment effects. Jump height variability is high in older people (35) as this is a novel task, consistent with physical activity not being a predictor in the regression analysis. The balance between fatigue and potential injury must be met with learning and repeatability, which may have limited our ability to detect treatment effects.

Declines in global measures of cognitive function, verbal memory, and executive function are associated with decreases in gait and predict gait speed decline in longitudinal studies (19). Declines in gait speed are also associated with impairments of multiple physiological systems (36). Overall, these studies and evidence from epidemiological studies suggest a range of underlying shared pathological processes, such as inflammation, hormonal imbalances, and vascular disease, contribute to declines in gait and cognition (37). It may therefore be that the improved HW speed may be related to the improvements in MOT and VRM, potentially via beneficial effects on some of these underlying processes. However, further work is needed to explore these effects.

Our hypothesis is that a combination of dietary factors has superior efficacy over individual nutrients, and successful nutritional interventions may require considerations of these synergistic interactions, as has also been found by others (38). However, a major

Table 1. Effects of Treatment on Cognition and Mobility

Variable	Baseline Mean (*SD*)	Six Months Mean (*SD*)	Adjusted Mean (*SD*)	*p* Value
Cognition				
MOT latency (ms)				
Placebo	1171 (276)	1162 (180)	1170 (162)	.038
Intervention	1171 (275)	1058 (190)	1052 (162)	
VRM immediate free recall (words)				
Placebo	9.2 (1.7)	8.0 (2.2)	7.7 (1.7)	.029
Intervention	8.7 (2.3)	8.8 (2.1)	9.0 (1.7)	
Mobility				
HW Speed (m/s)				
Placebo	1.35 (0.20)	1.32 (0.15)	1.29 (0.08)	.031
Intervention	1.30 (0.24)	1.33 (0.25)	1.36 (0.10)	

Note: FW = fast walking; HW = habitual walking; MOT = motor screening task; VJH = vertical jump height; VRM = verbal recognition memory.

unifying factor in the intervention is DHA. To identify the contribution of DHA, correlations were performed at baseline, where significant relationships were seen with DHA and all measures of mobility, consistent with previous observations (4). There is growing interest in identifying potential blood biomarkers for the detection and monitoring of physical performance in aging (39), and these results suggest that DHA status may provide useful further information.

Table 2. Effects of Treatment on Cadence and Stride Length

Variable	Baseline Mean (*SD*)	Six Months Mean (*SD*)	Adjusted Mean (*SD*)	*p* Value
HW cadence (steps/min)				
Placebo	116.3 (6.9)	114.8 (5.2)	113.7 (4.8)	.118
Intervention	114.1 (8.8)	115.1 (10.4)	116.0 (4.8)	
HW stride length (m)				
Placebo	1.38 (0.14)	1.38 (0.12)	1.36 (0.06)	.064
Intervention	1.35 (0.21)	1.38 (0.21)	1.39 (0.05)	
FW cadence (steps/min)				
Placebo	134.9 (6.0)	134.5 (7.3)	130.3 (7.6)	.065
Active	130.3 (7.0)	131.7 (13.9)	135.1 (7.6)	
FW stride length (m)				
Placebo	1.53 (0.15)	1.48 (0.22)	1.47 (0.12)	.100
Intervention	1.53 (0.24)	1.53 (0.24)	1.53 (0.12)	

Note: FW = fast walking; HW = habitual walking.

Correlations between changes in DHA levels and changes in mobility and cognition were performed at the end of the study, where there were significant associations between changes in DHA levels and improvements in mobility, which were primarily driven by the high-change DHA group. This suggests there was a subgroup more responsive to the supplementation, consistent with the observations of others (40). With cognition, AA:DHA was a stronger predictor of performance, where there were indications of a lower AA:DHA (ie, greater DHA to AA) to perform better in the VRM immediate free recall test. The difference in prognostic value between DHA levels and AA:DHA may depend on which tissue is being examined, and as although blood DHA levels show strong correlations with peripheral tissues, they may not reflect the composition of the brain (41).

The strength of this study is that it was of a randomized, placebo-controlled double-blind design. The high retention rate further increased the reliability of the data. Furthermore, the study used a range of detailed and sensitive mobility and cognitive tests to assess the treatment effects. However, a limitation of the study was that in some of the tests, a ceiling effect may have been observed due to the high ability of the participants. A further limitation was that neither plasma homocysteine levels nor ApoE genotypes were assessed, which may have affected the participant's response to treatment.

Conclusion

In this pilot study, a multinutrient supplement improves psychomotor reaction speed, verbal memory, and HW speed. These improvements were clinically relevant and were identified in able persons. It must be acknowledged that this pilot study was not adequately powered for direct comparisons between treatment groups, and effects were only seen in some of the primary outcomes; however, there were clear indications that supplementation improves cognition and mobility, which are of major importance in successful aging. The study also identified important relationships between blood DHA levels and mobility. Further work should seek to explore the long-term effects and whether the results can be extended to those with cognitive or mobility impairments.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

Table 3. Pearson's Partial Correlations Between DHA Status, Mobility, and Cognition at Baseline

Variables	AA:DHA	Grip (kg)	HWS (m/s)	FWS (m/s)	VJH (mm)	MOT* (ms)	VRM† (words)	PAL‡ (errors)	SOC§ (solved)
DHA	−.892***	.372	.465**	.552***	.498***	.049	−.161	.055	.033
AA:DHA		−.364	−.538***	−.618***	−.337	−.092	.217	.089	−.012
Grip (kg)			.148	.265	.198	.175	−.095	.184	.056
HWS (m/s)				.877***	.493***	−.066	.099	−.206	.160
FWS (m/s)					.552***	.124	.116	.050	.222
VJH (mm)						.003	.039	.049	.378
MOT† (ms)							.348	−.243	−.052
VRM‡								.151	.160
PAL§									.169

Notes: AA = arachidonic acid; DHA = docosahexaenoic acid; FWS = fast walking speed; Grip = grip strength; HWS = habitual walking speed; MOT = motor screening task; PAL = paired associate learning; VJH = vertical jump height; VRM = verbal recognition memory.

*Latency.

†Immediate free recall.

‡Eight pattern.

§Problems solved.

$^{**}p < .05$, $^{***}p < .01$.

Table 4. Multiple Regression Models Showing Significant Associations With Mobility at Baseline

Variable	β	95% Confidence Intervals	*p* Value
HW Speed (m/s)			
DHA (wt%)	0.102	0.041, 0.162	.002
PASE score	0.003	0.001, 0.004	.001
FW Speed (m/s)			
PASE score	0.002	0.000, 0.004	.047
DHA (wt%)	0.141	0.069, 0.214	<.001
VJH (mm)			
Age (y)	−0.319	−0.541, −0.098	.007
DHA (wt%)	1.921	0.717, 3.125	.003
BMI (kg/m^2)	−0.761	−1.157, −0.366	.001

Note: BMI = body mass index; DHA = docosahexaenoic acid; FW = fast walking; HW = habitual walking; PASE = Physical Activity Scale of the Elderly; VJH = vertical jump height.

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Conflict of Interest

The authors declare no conflicts of interest.

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