Clinical Interventions in Aging

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ORIGINAL RESEARCH

Dietary Supplement Intake and Its Association with Cognitive Function, Physical Fitness, Depressive Symptoms, Nutritional Status and Biochemical Indices in a 3-Year Follow-Up Among Community Dwelling Older Adults: A Longitudinal Study

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Purpose: Use of dietary supplements by older adults has been increasing for improving micronutrient deficiencies, cognitive function, and overall health status. Thus, the objective of this secondary investigation is to explore the longitudinal association of baseline supplement intake in improving cognitive function, biochemical parameters, anthropometric variables and physical fitness among older adults.

Methods: Towards Useful Aging (TUA) is a three-year longitudinal study conducted at baseline (2013–2014) and at follow-up (2015–2017) surveys. The number of participants dropped from 2322 during baseline study to 1787 and 1560 during the 18th and 36th month follow-up, respectively. Data on socio-demography, use of dietary supplement, biochemical indices, anthropometry, cognitive function, physical fitness and depressive symptoms were obtained. Longitudinal associations were done using the linear mixed model analysis among 1285 subjects with complete data.

Results: The most common vitamin and mineral supplementations consumed were multivitamin, B-complex, and calcium. Meanwhile, the herbal supplements consumed by participants were *Eurycoma longifolia, Morinda citrifolia* and *Orthosiphon aristatus*. Longitudinal analysis adjusted for multiple covariates showed improvement in both supplement users and non-users for global cognitive function, working memory, visual memory, 2-minute step test, chair stand test, chair sit and reach and time up and go test, waist circumference and hip circumference in both the supplement users and non-users.

Conclusion: Our findings indicated that dietary supplement intake is not associated with cognitive function, physical fitness, nutritional status, depressive symptoms or biochemical indices since improvement in the parameters was observed among both supplement users and non-users.

Keywords: dietary supplement, cognitive function, physical fitness, depressive symptoms, nutritional status, biochemical

Plain Language Summary

The study was done to identify the longitudinal association between dietary supplement intake with cognition, physical fitness, nutritional status, depressive symptoms and biochemical parameters. For this purpose, we have conducted a 3-year longitudinal study among individuals aged 60 years and above who were community dwellers and free from dementia. The most commonly consumed dietary supplements by older adults were multivitamin, B-complex,

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and calcium while herbal supplements were *Eurycoma longifolia* and *Morinda citrifolia*. Linear mixed model analysis showed that that baseline vitamin, mineral or herbal supplement intake showed significant improvement in most of the investigated parameters after three years. Similar improvement was also observed in the control group indicating presence of practice effect. Hence, the findings from this study demonstrated that dietary supplement intake will not provide health benefit to older adults. Thus, older adults must not rely on dietary supplements alone whilst neglecting healthy diet and lifestyle. Supplement intake is possible with the advice of physician.

Introduction

Longer life expectancy increases the expenditure for hospital treatments, pensions, social security and long-term care.[1] Although lifespan has increased, there is a marked decline in health expectancy by 8 to 11 years, suggesting that older adults may suffer from neurodegenerative diseases or disability during their last decades of life.[2] Longer life expectancy may increase the incidence of mild cognitive impairment (MCI), a prodromal stage of dementia. Untreated MCI, over time, may promote incidence of dementia whereby 13% of older adults aged 72 years old and 32% of older individuals have dementia and Alzheimer`s Disease (AD) respectively.[3]

Rising prevalence of dementia has driven the World Health Organization (WHO) to declare dementia as a public health concern.[4] Approximately 47 million people are diagnosed with dementia worldwide and this incidence is expected to double with every 5.9-year increase in age, from 3.1 per 1000 person years at age 60–64 years old to 175 per 1000 person years at age 95 years or above.[5] In Malaysia, the prevalence of mild cognitive impairment and cognitive pre-frailty as risk factors of dementia are 16% and 37.4%.[6,7] The negative consequences of cognitive impairment are disability, poor quality of life, social isolation, depression and hospitalization. Depression is another issue among older adults which will affect their nutritional status. Depression is especially prevalent among older adults with dementia, and those living alone or in an institution.[8]

The presence of these driving factors lead to several physiological changes contributing to undernutrition such as malabsorption, poor utilization of nutrients and chronic diseases as well loss of appetite, changes in dietary habits, food-drug interaction, inability to prepare meals or purchase food or loss of interest in food consumption. Persistent micronutrient deficiencies may deteriorate the health of older adults contributing to adverse effects such as frailty, hospitalization and increased mortality.[9,10]

Over the past years, older adults started using dietary supplementation due to the perception that it may improve their health status such as reducing risk of chronic diseases.[11] Dietary supplements can be any product used to supplement the diet which may consist of any one or more of the dietary ingredients such as vitamins, minerals, herbs, amino acid or botanical compounds to meet an individual`s nutritional requirements.[12,13] In Malaysia, there is a high use of dietary supplements as an adjunct treatment for chronic diseases.[14]

The purpose of this secondary investigation was to assess the longitudinal association between dietary supplementation (either vitamin, mineral or herbal) use at baseline in improving various parameters namely cognitive function, physical fitness, anthropometry and biochemical at 18 and 36 months, among community dwelling older adults in Malaysia.

Methodology

Study Design and Sampling Strategy

The present data are part of a three-year longitudinal Towards Useful Aging (TUA) study conducted among 2322 community dwelling older adults in four selected states in Malaysia with the highest number of older adults; namely, Perak (northern region), Kelantan (eastern region), Klang Valley (central region) and Johor (southern region). The study has two follow-ups at the 18th and 36th month after the baseline study. A total of 1787 and 1560 participants attended the 18th month and 36th month study yielding a response rate of 77% and 67.2% respectively. Among the reasons for loss of follow-up during the 18th and 36th month were refusal of participants to join, ill health, mortality, migration to another state, or failure to be contacted due to changes in contact number and home address. Hence, to reduce the risk of bias, only participants who managed to be recruited for all three follow-ups were included for the longitudinal analysis.

Multi-stage random sampling method was employed as the sampling method of this study with the assistance of the Department of Statistics Malaysia. The methodology of this study was described in detail in previous publication.[15,16] Recruitment of participants was conducted in three stages namely primary sampling unit (PSU), secondary sampling unit (SSU) and tertiary sampling unit (TSU). PSU involved the selection of states with the highest number of geriatric citizens; followed by selection of 35 census circles within each state in the SSU stage. The census circle selected had at least 10% of elderly population. Finally, in TSU, each census circle is further divided into 20 living quarters and eligible participants were selected within the living quarters.

Ethical Approval and Informed Consent

This study has been performed in accordance with the principles stated in the Declaration of Helsinki. This study has obtained ethical approval from the Research and Medical Research Ethics Committee of Universiti Kebangsaan Malaysia. The ethical approval number was LRGS/BU/2012/UKM-UKM/K/01. Prior to subject's recruitment, informed consent were acquired from each individual. For those who are illiterate, thumb print was obtained.

Consent for Publication

All participants provided consent for publication. Names and address of patients will not be revealed in the published materials.

Participant Selection

Individuals selected for this study met several inclusion criteria: aged 60 years and above, Malaysian citizen, not wheel-chair bound, no major psychiatric illnesses such as schizophrenia, bipolar disorder or hallucination, not being diagnosed with debilitating illnesses such as cancer on treatment, all types of dementia, communicable diseases such as AIDS, tuberculosis or hepatitis. Meanwhile, the exclusion criteria were individuals with moderately severe or severe cognitive impairment based on the Mini-Mental State Examination (MMSE) score of 14 and above.[17]

Supplement Intake

Participants were asked if they consumed any dietary supplements for the past one month. Supplementation consists of any vitamin, mineral or any traditional herbs.

Outcome Measures and Measurement Tools

The instruments described below except biochemical parameters were administered at baseline, 18th month and 36th month. This is parallel with several longitudinal studies which repeated the cognitive test batteries after one or two years from the duration of baseline study involving older individuals.[18,19] It is undeniable that there will be practice effect in longitudinal studies due to multiple administration. Although the current study is unable to totally eliminate the practice effects, we have taken attempts to reduce it by removing outliers and adjusting the statistical model for multi-covariates.

The parameters investigated in this study were socio-demographic, anthropometry, dietary history, cognitive assessment, and physical fitness. Socio-demography parameters included age, gender, education years, household income, smoking status and alcohol consumption.

Anthropometry consists of weight, mid-upper arm circumference, waist circumference and hip circumference were measured according to standard techniques.[16] Weight was measured using the SECA Digital Lithium Weighing Scale. Prior to weight measurement, participants were asked to empty their pockets and remove their watches, cap or belt. Participants were required to stand straight with arms hanging freely at the sides of body. Weight measurement was taken twice at the nearest 0.1kg. Meanwhile, waist and hip circumference was measured using a flexible Lufkin tape. Waist circumference was measured midway between the lowest rib and the iliac crest. The tape should not be tight till compressing the skin of the participants. Measurements were taken at the end of a normal expiration to the nearest 0.1cm. On the other hand, hip circumference measurement was taken at the largest part of the buttock to the nearest 0.1cm.

Besides that, depressive symptoms were assessed using the 15-item Geriatric Depression Scale (GDS).[20] In this questionnaire, each item had a binary answer option of "Yes" or "No". A higher score indicated greater severity of depressive symptoms. GDS score ranged from minimum of 0 to maximum of 15. A score of four and below indicated no depressive symptoms.

Cognitive assessment was conducted using various cognitive test batteries such as Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCa), Digit Symbol, and Digit Span, Visual Reproduction I & II. MMSE was used for assessing global cognitive function. MMSE consists of 12 items which measures domains of orientation, language, attention, memory and visual construction.[21] Its score ranged from zero to 30. The higher score indicated better cognitive functioning. Besides that, MoCA was another screening tool for measuring attention, executive function, memory, language, orientation and visuo-construction skills.[22] MoCA had better diagnostic accuracy as compared to MMSE in distinguishing between individuals with Alzheimer`s disease and mild cognitive impairment (MCI).[23] Time for MoCA administration was about 10 minutes and the maximal score was 30.

On the other hand, Digit Span was a test for assessing working memory and attention. It consists of two sections; forward and backward test. In forward digit span test, participants were required to remember and recall the numbers stated by the researcher in the correct order, while the backward test involved the repetition of the number sequence in the reverse order. Score for Digit Span test was the total of both the forward and backward test.[24] Besides that, Digit Symbol test is a paper and pencil test for measuring processing speed. In this test, participants were required to match symbols to the respective number provided in the sheet within 120 seconds. Participants with a higher score show good motor speed and visuoperceptual function.[25] Visual Reproduction I

& II were tests for measuring visual memory. In this test, subjects were required to observe and draw four printed geometric pictures shown. In VR1, pictures were shown one at a time for 30 seconds and they were required to draw on the space given.[25]

A total of six physical fitness tests were conducted, namely 2-minute step test, hand grip strength, chair sit and reach test, back scratch test, gait speed and timed up and go test. The 2-minute step test was for assessing endurance and aerobic capacity. In this test, participants were required to march for two minutes, while in the hand grip strength subjects were required to grip the hand held dynamometer as tight as they could to assess their upper muscular strength. When assessing hand grip strength, participants were required to sit straight in a chair without an arm rest with hand flexed at 90 degrees. Dominant hand used for daily routine was chosen to be tested. A total of two readings were obtained. The second reading was taken after 30 seconds of rest after the first test. Results were recorded to the nearest kg. Besides that, in timed up and go test, participants were required to walk to and fro for three meters from a seated position. Stopwatch was started the moment the subject stood from the chair and timer was stopped when they were seated in the original position. A shorter time for completing this task indicated good balance and lower risk of falls. However, several precautions were considered for this test to avoid falls such as the use of a stable chair, conducting the test on a smooth surface, and ensuring that participants were wearing suitable footwear or clothing.

Chair stand test assessed lower body strength, and, in this test, participants were required to raise and sit in a chair repetitively for a period of 30 seconds. The number of attempts within the given duration was recorded. A chair without arm rests was used for this test. Researcher had to ensure that the chair used was placed against the wall to minimize fall risk and accidental injuries. Chair sit and reach test was for testing lower body flexibility. In this test, participants in seated position were required to straighten their leg and, without bending the knees, participants needed to touch their toes. The smaller distance between the toes and fingers indicated good flexibility. Lastly, back scratch test was for measuring upper body flexibility. Participants were required to place one of their hands above their head and behind the body, while another hand being placed below the body. Attempt had to be made to join both hands. Smaller distance between both hands indicated good flexibility.

Biochemical parameters include fasting blood glucose and serum lipid profile which consisted of total cholesterol, high density lipoprotein (HDL-C), low density lipoprotein (LDL-C) and triglyceride. A total of 20 mL blood was withdrawn by a trained phlebotomist which would be analysed in the nearest laboratory. Participants were asked to fast overnight for the purpose of blood withdrawal. Biochemical data was only available for selected participants at the baseline and 36th month follow-up study.

Statistical Analysis

Descriptive statistics was used for presenting data on types of supplements consumed by the participants. Independent *t*-test and Chi-Square test were employed for determining the mean difference and association during the baseline study. Mixed linear models were used to examine the longitudinal association between the outcome variables and baseline dietary supplement intake. Results were reported as estimates with 95% confidence interval (CIs). The dependent variables for the linear mixed model analysis were numerical. The linear mixed models were adjusted for covariates such as age, gender, education years, smoking status, calf circumference, hand grip strength, chair sit and reach test, digit span, MMSE, GDS, VRI and VRII. These variables were chosen as covariates as they had significant association between supplement takers and non-takers during the baseline analysis. Linear mixed models analysis was conducted among 1285 subjects, obtained after removing the outliers of the outcome variables as well as excluding subjects who failed to participate during the follow-up phases. Missing values for each variable were coded as 888 in the PASW dataset. For each variable, significance was set at $p<0.05$.

Results

Baseline Characteristics of Users and Non-Users of Dietary Supplement

Analyses in Table 1 were conducted between users and non-users of vitamin/mineral and herbal supplements. Generally, 29.1% and 20.7% of the participants consumed vitamin/mineral and herbal supplements at baseline, respectively. Table 1 shows the baseline characteristics of the participants which shows more women (57.3%) compared to men (42.7%) consume vitamin or mineral supplementations (p<0.05). Non-smokers (78.2%) were reported to have higher intake of vitamin or mineral supplementation as

Table 1 Baseline Characteristics of Participants [Presented as n(%) or Mean±Standard Deviation]

	Consume Vitamin and Mineral Supplements		**Consume Herbal Supplement**	
	Yes (n=665)	**No (n=1622)**†	**Yes (n=389)**	**No (n=1880)**†
Gender				
Men	284 (42.7)	812 (50.1)**	225 (57.8)	863 (45.9)***
Women	381 (57.3)	810 (49.9)	164 (42.2)	1017 (54.1)
Age, years	70.0±6.1	69.1±6.3	68.2±5.8	69.2±6.3***
Education years	6.47(4.41)	4.61(3.68)	5.88(3.75)	5.00(4.02)
Race				
Malay	388 (58.3)	1043(64.3)***	293 (75.3)	1123(59.7)***
Chinese	225 (33.8)	511 (31.5)	90 (23.1)	642 (34.1)
Indian	48 (7.2)	67 (4.1)	5 (1.3)	111(5.9)
Others	4 (0.6)	1 (0.1)	1 (0.3)	4 (0.2)
Family history of dementia				
Yes	49 (7.4)	115 (7.1)	35 (9.0)	128 (78.5)
No	578 (86.8)	1408 (86.8)	337 (86.6)	1631 (86.8)
Not sure	38 (5.7)	99 (6.1)	17 (12.3)	121 (87.7)
Smoking Status				
Smoker	68 (10.2)	324 (20.0)***	72 (18.5)	315 (16.8)**
Ex-smoker	77 (11.6)	212 (13.1)	68 (17.5)	217 (11.5)
Non-smoker	520 (78.2)	1086 (67.0)	249 (64.0)	1348 (71.7)
Alcohol				
Yes	32 (4.8)	61 (3.8)	12 (3.1)	81 (4.3)
No	633 (95.2)	1561 (96.2)	377 (96.9)	1799 (95.7)
Hip Circumference, cm	97.27±9.60	96.15±9.50*	97.4±9.8	96.3±9.5
Waist circumference, cm	88.23±11.31	88.22±11.24	89.3±11.1	88.1±11.3
Calf circumference, cm	28.49±3.63	28.39±3.43	29.0±3.4	28.3±3.5***
Hand grip, kg	22.84±7.71	23.20±7.95	24.4±7.7	22.8±7.9***
Chair stand test, count	10.34±3.20	9.77±3.12***	10.2±2.9	9.9±3.2
Chair sit and reach test, cm	1.28±11.56	1.68±11.98	0.04±11.5	1.9±12.0**
TUG, seconds	10.53±3.30	11.24±3.29***	10.8±3.0	11.1±3.4
Back Scratch Test, cm	13.63±12.55	16.01±12.81***	14.5±12.3	15.5±12.9
Digit span	7.96±2.46	7.29±2.40***	7.89±2.44	7.40±2.42***
MMSE	23.92±4.69	22.36±4.91***	23.91±4.12	22.60±5.01***
Digit symbol	5.81±2.99	4.53±2.21***	5.04±2.39	4.90±2.56
GDS	2.46±2.08	2.80±2.35**	2.40±2.09	2.74±2.29**
VR I	52.32±33.43	38.83±31.92***	46.2±32.5	42.1±33.0*
VRII	45.04±37.57	30.64±32.78**	33.9±34.5	39.4±36.3*

Notes: Significant at ***p<0.001; **p<0.01; *p<0.05. †Only 2287 and 2269 data were available for vitamin/mineral and herbal supplement intake respectively. Remaining were missing data. Chi-Square test employed when both variable were categorical. Independent-*t*-test for numerical dependent variable.

Abbreviations: TUG, timed up and go test; MMSE, Mini Mental State Examination; VRI, Visual Reproduction I; VRII, Visual Reproduction II; GDS, Geriatric Depression Scale.

compared to smokers (10.2%). At baseline, participants who took vitamin or mineral supplementations had larger hip circumference, better score in chair stand test, TUG, MMSE and digit span than those who did not take the supplements (p<0.05 for all parameters). Further, consumption of herbal supplements was higher among men (57.8%) and non-smokers (64.0%) as compared to 42.2% in women and 18.5% in smoker (p<0.05 for both parameters). Participants who took herbal supplements also had a higher education level, hand grip strength, calf circumference, digit span, MMSE and VRI (p<0.05) as compared to non-users (Table 1).

Types and Frequency of Supplement Intake at Baseline

Table 2 shows the types of supplementation consumed by participants during the baseline study. Each participant may consume more than one type of supplement. Vitamin and mineral supplementations most commonly consumed by participants were multivitamin, vitamin B-complex, calcium, vitamin C and fish oil. Meanwhile, the type of herbal supplements consumed by participants were local Malaysian herbs such as Tongkat Ali (*Eurycoma longifolia*), mengkudu (*Morinda citrifolia*), Misai Kucing (*Orthosiphon aristatus*), jamun (*Syzygium umini*), Habbatus sauda (*Nigella sativa*) and gamat (*Holothuroidea*).

Longitudinal Analysis for the Association Between Baseline Intake of Vitamin/Mineral Supplementation with Cognitive Function, Physical Fitness, Anthropometry and Biochemical Indices

Table 3 shows the longitudinal association between vitamin/mineral supplement intake with cognitive function, depressive symptoms, physical fitness, anthropometry and biochemical indices. In a fully adjusted model, using the 36th month scores as reference, there is an increasing trend between the supplement users and non-users for the MMSE (estimate: −1.22; 95% CI: −1.78,0.67) (p<0.001), digit span (estimate: −1.11 (95% CI: −1.56,-0.66)) (p<0.001) and VRI scores (estimate value of −10.47 (95% CI: −15.41, −5.17)) (p<0.001). The multivariable adjusted rate for MoCA scores significantly increase from the 18th month to 36th month for both groups (estimate: −1.13 (95% CI: −1.92, −0.35)) (p=0.005).

Table 2 Baseline Dietary Supplementation Consumed by Participants

Type of Supplement	Number of Participants* Consuming Supplement (n)	%
Vitamin/Mineral		
Multivitamin	137	20.60
B-complex	88	13.23
Calcium	99	14.89
Vitamin E	25	3.76
Zinc	3	0.45
Vitamin C	85	12.78
Selenium	1	0.15
Fish Oil	88	13.23
Lecithin	3	0.451
Evening Primrose	6	0.90
Herbal Supplement		
Spirulina	17	4.37
Gamat	6	1.54
Shark Fin	1	0.26
Chinese Traditional Medicine	8	2.06
Bird Nest	1	0.26
Ginseng	7	1.80
Gingko Biloba	7	1.80
Kacip Fatimah	8	2.06
Ginger tablet	12	3.08
Garlic tablet	14	3.60
Tongkat Ali	21	5.50
Mengkudu	3	0.77
Misai Kucing	10	2.57
Majun	15	3.86
Jamun	2	0.51
Lidah Buaya	1	0.26
Habbatus Sauda	12	3.08
Manjakani	1	0.26
Not knowing the name of supplement	122	31.36

Note: *Each subject may take one or more vitamin, mineral or herbal supplement.

Meanwhile, the multivariable adjusted rate for GDS score for depressive symptoms indicated lower baseline score as compared to the 36th month score with an estimate value of −0.36 (95% CI: −0.69, −0.04) (p=0.03) for both the supplement users and non-users.

Similarly, for the fully adjusted model with 36th month score as reference, the 2 minute step test (estimate:-10.82; 95% CI: −14.34, −7.31)(p<0.001) and chair stand test (estimate: −0.43, 95% CI:-0.86,-0.00) (p<0.001) showed significantly better score at 36th month as compared to baseline and 18th month follow-up for both groups. On the

Table 3 Longitudinal Association Between Baseline Vitamin/Mineral Supplement Intake with Cognitive Function, Physical Fitness, Anthropometry and Biochemical Indices (N=1285)

Parameter	Vitamin/Mineral Intake		Coefficient for Time (95% CI)	p for Trend*
	Yes	No		
Cognitive Function and Depressive Symptoms				
MMSE				
Baseline	24.74 (3.76)	23.63(4.15)	−1.22 (−1.78,0.67)	p<0.001
18th month	25.23(3.51)	24.18(3.47)	−0.74 (−1.32,0.16)	0.012
36th month	25.97(3.79)	24.92(3.61)	0	
MoCA				
Baseline	21.42(4.66)	19.42(5.20)	−0.25 (−1.01,0.51)	0.520
18th month	20.54(5.33)	18.47(5.63)	−1.13 (−1.92,-0.35)	0.005
36th month	21.67(5.16)	20.12(4.97)	0	
Digit span				
Baseline	8.16(2.29)	7.72(2.37)	−1.11(−1.56,-0.66)	p<0.001
18th month	8.11(2.45)	7.85(2.36)	−1.16 (−1.63,-0.70)	p<0.001
36th month	9.27(6.20)	8.54(2.77)	0	
Digit symbol				
Baseline	6.03(3.01)	4.83(2.23)	−0.22 (−0.64, 0.20)	0.297
18th month	6.14(3.40)	4.82(2.81)	−0.12 (−0.55,0.31)	0.581
36th month	6.26(3.37)	4.75(2.50)	0	
VR1				
Baseline	56.10(33.06)	42.60(32.63)	−1.75(−6.72,3.22)	0.489
18th month	47.56(34.96)	36.93(31.93)	−10.47(−15.41,-5.17)	<0.001
36th month	57.85(34.93)	44.12(33.51)	0	
GDS				
Baseline	2.28(1.99)	2.53(2.24)	−0.36(−0.69,-0.04)	0.030
18th month	2.74(2.35)	2.94(2.22)	−0.09(−0.25,0.43)	0.586
36th month	2.65(2.15)	2.93(2.25)	0	
Physical Fitness				
2minstep test				
Baseline	65.68(26.23)	63.73(24.60)	−10.82(−14.34,-7.31)	<0.001
18th month	61.84(22.66)	61.59(21.59)	−14.66(−18.33,-11.00)	<0.001
36th month	76.50(23.05)	73.90(21.37)	0	
Chair stand test				
Baseline	10.52(3.17)	10.18(3.03)	−0.43(−0.86,-0.00)	<0.001
18th month	10.41(2.71)	10.03(2.82)	−0.75(−1.22,-0.74)	<0.001
36th month	11.19(2.83)	10.67(2.54)	0	
Handgrip strength				
Baseline	23.31(7.55)	24.43(7.77)	−0.66(−1.79, 0.47)	0.25
18th month	23.05(7.49)	23.58(7.79)	−0.92 (−2.08,0.27)	0.12
36th month	23.97(7.08)	24.86(7.26)	0	
Chair Sit and Reach				
Baseline	0.66(11.13)	0.36 (11.16)	−2.36(−4.04,-0.67)	0.006
18th month	2.10(10.05)	2.70(10.61)	−0.91(−2.65,0.82)	0.303
36th month	3.01(11.50)	3.74(12.51)	0	
Time Up and Go				
Baseline	10.09(2.95)	10.62(2.84)	−0.86(−1.31,-0.39)	<0.001
18th month	10.86(3.05)	11.38(2.92)	0.08(−0.56,0.39)	0.74

(*Continued*)

Table 3 (Continued).

Parameter	Vitamin/Mineral Intake		Coefficient for Time (95% CI)	p for Trend*
	Yes	No		
36th month	10.94(3.39)	11.53(3.37)	0	
Back Scratch test				
Baseline	13.08(12.71)	14.95(12.73)	−0.51 (−2.44, 1.42)	0.61
18th month	14.18(11.33)	15.85(11.65)	0.59 (−1.40, 2.58)	0.56
36th month	13.59(13.96)	16.68(14.10)	0	
Anthropometry				
Weight				
Baseline	61.70(12.06)	61.84(11.98)	0.08(−1.90,1.73)	0.93
18th month	62.26(12.40)	61.64(12.12)	0.48(−1.39, 2.35)	0.62
36th month	61.78(12.52)	60.39(12.01)	0	
Waist circumference				
Baseline	88.56(11.52)	88.48(11.45)	2.88(1.08,4.67)	0.002
18th month	83.22(12.34)	82.96(12.22)	−2.47(−4.32,-0.62)	0.009
36th month	85.68(12.47)	84.31(12.21)	0	
Hip Circumference				
Baseline	97.60(9.59)	96.57(9.32)	1.96 (0.46,3.46)	0.01
18th month	95.65(11.05)	93.70(9.47)	0.01 (−1.54,1.56)	0.99
36th month	95.63(10.90)	93.71(10.69)	0	
MUAC				
Baseline	28.77(3.69)	28.72(3.25)	−0.16(−1.11,0.80)	0.75
18th month	27.80(3.74)	27.62(3.23)	−1.13(−2.12,-0.14)	0.03
36th month	28.93(3.64)	29.32(12.17)	0	
Calf circumference				
Baseline	34.01(3.79)	33.56(3.69)	−0.60(−1.56,0.37)	0.23
18th month	33.74(4.06)	33.31(3.60)	−0.86(−1.86,0.14)	0.09
36th month	34.60(9.55)	33.94(10.45)	0	
Biochemical**				
Glucose				
Baseline	6.01(2.04)	6.13(2.13)	−1.14(−0.50,0.22)	0.31
36th month	6.14(2.23)	6.31(2.40)	0	
Total cholesterol				
Baseline	5.47(1.16)	5.49(1.12)	0.03(−0.15,0.22)	0.75
36th month	5.21(1.20)	5.24(1.06)	0	
HDL cholesterol				
Baseline	1.44(0.35)	1.39(0.35)	0.02(−0.04,0.07)	0.59
36th month	1.43(0.37)	1.39(0.36)	0	
LDL cholesterol				
Baseline	3.18(1.00)	3.41(1.01)	0.08(−0.10,0.25)	0.37
36th month	3.36(1.03)	3.10(1.11)		
Triglyceride				
Baseline	1.39(0.59)	1.54(0.78)	−0.14(−0.27, −0.01)	0.03
36th month	1.52(0.73)	1.62(0.86)		

Notes: *p<0.05 for the longitudinal analysis between users and non-users of herbal supplements. The model is fully adjusted for covariates such as such as age, gender, education years, smoking status, calf circumference, hand grip strength, chair sit and reach test, digit span, MMSE, GDS, VRI and VRII. **For biochemical data, data were only available at baseline and 36th month for selected participants (324 for baseline and 687 for 36th month).

Abbreviations: Ref, reference group; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; VRI, Visual Reproduction I; VRII, Visual Reproduction II; GDS, Geriatric Depression Scale; MUAC, mid-upper arm circumference; HDL, high density lipoprotein; LDL, low density lipoprotein.

other hand, for both vitamin and mineral supplement users and non-users, the scores for chair sit and reach test (estimate: −2.36, 95% CI: −4.04,-0.67) as well as time up and go test (estimate: −0.86, 95% CI: −1.31, −0.39) showed significant increase from the baseline to the 18th month which indicated declining lower body flexibility and mobility.

As for anthropometric parameters with 36th month as reference group, multivariable adjusted rate for waist circumference showed decreasing trend from baseline to the 36th month with estimate value of 2.88 (95% CI: 1.08, 4.67) ($p<0.002$) for both supplement users and non-users. Meanwhile, hip circumference adjusted rates increased from baseline to the 18th month, 1.96 (95% CI: 0.46, 3.46) ($p<0.01$). Meanwhile, multivariable adjusted rate for MUAC for both the groups (estimate: −0.16, 95% CI: −2.12, −0.14) ($p=0.03$) showed significant increase from the 18th month to the 36th month.

On the other hand, the biochemical data was only available for certain participants during the baseline and 36th month follow-up. With the 36th month value as reference, the triglyceride value at baseline was lower as compared to the 36th month (estimate: −0.14, 95% CI: −0.27, −0.01) ($p=0.03$) for both supplement users and non-users. However, the values were still within the normal range for triglyceride.

In summary, baseline intake of vitamin and mineral supplementation was not associated with improvement in the observed parameters since positive changes were also observed among the control group.

Longitudinal Analysis for the Association Between Baseline Intake of Herbal Supplementation with Cognitive Function, Physical Fitness, Anthropometry and Biochemical Indices

Overall, results in Table 4 show that both the baseline herbal supplement users and non-users had significant improvements in most cognitive and physical function tests after the model has been adjusted for covariates, which indicated that herbal supplement use had no effect on the observed parameters.

Using the 36th month as the reference group, the MMSE (estimate:-1.12, 95% CI: −1.66,-0.58) ($p<0.001$) and digit span (estimate: −1.11, 95% CI: −1.56, −.0.66) ($p<0.001$) showed significantly increasing trend from baseline to the 36th month among supplement users and non-users. The multivariable adjusted rate for MoCA (estimate:-1.05, 95% CI: -1.83, -0.27) showed significantly increasing trend from the 18th month to the 36th month ($p<0.05$) among both the herbal supplement users and non-users. Meanwhile, VRI score (estimate: 29.92, 95% CI: 25.80, 34.04) showed decreasing pattern from baseline to the 36th month ($p<0.01$) in both the groups. Similarly, the supplement users and non-users showed significantly increasing multivariable adjusted rate from baseline to the 18th month for GDS (estimate: −0.39; 95% CI: −0.72, −0.05) ($p=0.02$).

For physical fitness components, multivariable adjusted rate for 2 minute step test (estimate: −10.84; 95% CI: −14.36, −7.31) ($p<0.001$) and chair stand test (estimate: −0.44, estimate: −0.87,-0.01) ($p=0.04$) increased significantly from baseline to 36th month. Multivariable adjusted rates for chair sit and reach (estimate: −2.59, 95% CI: −4.28,-0.91) ($p<0.001$) and time up and go tests (estimate:-0.93, 95% CI: −1.39, −0.47) ($p<0.001$) scores showed significant increase from baseline to 18th month among both the supplement users and non-users.

Multivariable adjusted rate for waist circumference decreased from baseline to 36th month for both the supplement users and non-users (estimate: 2.97, 95% CI: 1.19, 4.76) ($p<0.001$). Among supplement users and non-users, hip circumference significantly decreased from baseline to 18th month (estimate: 1.97; 95% CI: 0.49, 3.46) ($p=0.009$), while MUAC increased from 18th month to 36th month (estimate: −1.12, 95% CI: −2.09, −0.14) ($p=0.02$).

Furthermore, only multivariable adjusted rates for triglyceride significantly increased from baseline to 36th month (estimate: −0.14; 95% CI: −0.27,-0.01) ($p=0.03$) for both the groups.

Discussion

The aim of this study is to explore the longitudinal association of baseline dietary supplement intake towards several parameters related to cognitive function, biochemical parameters, nutritional status, physical fitness and depressive symptoms. During the baseline study, a total of 2322 subjects were recruited, however at the 18th and 36th month follow-up, there was a drastic drop to 1787 and 1560 people respectively. Thus, for reducing the impact of attrition or managing the sample bias during data analyses, participants who failed to join during the follow-up phases were excluded and the outliers for the outcome variables were removed.[26] Loss of follow-up were due to mortality,

Table 4 Longitudinal Association Between Baseline Herbal Supplement Intake with Cognitive Function, Physical Fitness, Anthropometry and Biochemical Indices (N=1285)

Parameter	Herbal Supplement Intake		Coefficient for Time (95% CI)	p for Trend*
	Yes	No		
Cognitive Function and Depressive Symptoms				
MMSE				
Baseline	24.82 (3.61)	23.80(3.65)	−1.12 (−1.66,-0.58)	p<0.001
18th month	25.20(3.50)	24.12(3.52)	−0.74 (−1.30,-0.18)	0.01
36th month	25.94(3.75)	24.81(3.76)	0	
MoCA				
Baseline	21.44(4.66)	19.43(5.04)	−0.12 (−0.87,0.64)	0.76
18th month	20.50(5.34)	18.94(5.19)	−1.05 (−1.83,-0.27)	0.01
36th month	21.55(5.20)	19.82(5.18)	0	
Digit span				
Baseline	8.14(2.31)	7.70(2.38)	−1.11(−1.56,-0.66)	p<0.001
18th month	8.10(2.44)	7.81(2.37)	−1.15 (−1.62,-0.69)	p<0.001
36th month	9.25(6.14)	8.44(2.79)	0	
Digit symbol				
Baseline	6.04(3.02)	4.78(2.22)	−0.14 (−0.56, 0.27)	0.50
18th month	6.13(3.40)	4.75(2.80)	−0.05 (−0.48,0.37)	0.81
36th month	6.19(3.37)	4.65(2.51)	0	
VR1				
Baseline	56.34(33.00)	42.37(32.47)	29.92 (25.80,34.04)	0.001
18th month	47.30(35.03)	36.23(31.86)	20.88(16.62, 25.13)	<0.001
36th month	26.42(10.08)	22.70(9.87)	0	
GDS				
Baseline	2.30(1.98)	2.60 (2.28)	−0.39(−0.72,-0.05)	0.02
18th month	2.73(2.33)	3.00(2.27)	0.05(−0.30,0.39)	0.79
36th month	2.69(2.19)	2.90(2.24)	0	
Physical Fitness				
Two-minute step test				
Baseline	65.30(26.31)	63.11(24.94)	−10.84(−14.36,-7.31)	<0.001
18th month	61.72(22.88)	60.99(21.91)	−14.41(−18.09,-10.74)	<0.001
36th month	76.14(23.55)	73.61(21.39)	0	
Chair stand test				
Baseline	10.70(3.19)	10.15(3.04)	−0.44(−0.87,-0.01)	0.04
18th month	10.41(2.71)	9.98(2.84)	−0.74(−1.19,-0.30)	0.001
36th month	11.15(2.83)	10.64(2.54)	0	
Handgrip strength				
Baseline	23.24(7.54)	24.27(7.85)	−0.70(−1.82, 0.43)	0.22
18th month	23.02(7.51)	23.42(7.81)	−0.92 (−2.08,0.25)	0.12
36th month	23.94(7.08)	24.69(7.31)	0	
Chair Sit and Reach				
Baseline	0.60(11.06)	0.76 (11.45)	−2.59(−4.28,-0.91)	0.003
18th month	2.09(10.02)	2.87(10.70)	−1.10(−2.84,0.64)	0.215
36th month	3.19(11.54)	3.94(12.50)	0	

(*Continued*)

Table 4 (Continued).

Parameter	Herbal Supplement Intake		Coefficient for Time (95% CI)	p for Trend*
	Yes	No		
Timed Up and Go				
Baseline	10.09(2.96)	10.69(2.95)	−0.93(−1.39,-0.47)	<0.001
18th month	10.86(3.04)	11.46(2.98)	−0.16(−0.64,0.32)	0.51
36th month	11.02(3.46)	11.58(3.36)	0	
Back Scratch test				
Baseline	13.19(12.66)	15.11(12.84)	−0.68 (−2.59, 1.26)	0.50
18th month	14.20(11.30)	15.93(11.70)	0.34 (−1.65, 2.32)	0.74
36th month	13.86(13.98)	16.68(14.23)	0	
Anthropometry				
Weight				
Baseline	61.57(12.06)	61.78(12.05)	−0.06 (−1.87,1.74)	0.94
18th month	62.20(12.40)	61.54(12.16)	0.55(−1.31, 2.42)	0.56
36th month	61.63(12.52)	60.38(11.99)		
Waist circumference				
Baseline	88.55(11.44)	88.42(11.51)	2.97(1.19,4.76)	0.001
18th month	83.13(12.37)	82.88(12.20)	−2.46(−4.30,-0.61)	0.01
36th month	85.58(12.54)	84.25(12.33)	0	
Hip Circumference				
Baseline	97.53(9.56)	96.61(9.36)	1.97 (0.49,3.46)	0.009
18th month	95.58(11.05)	93.74(9.52)	0.20(−1.52,1.56)	0.98
36th month	95.56(10.91)	93.77(10.64)	0	
MUAC				
Baseline	28.74(3.69)	28.72(3.34)	−0.16(−1.10,0.78)	0.74
18th month	27.78(3.73)	27.59(3.27)	−1.12(−2.09,-0.14)	0.02
36th month	28.90(3.65)	29.28(11.94)	0	
Calf circumference				
Baseline	33.97(3.78)	33.58(3.69)	−0.56(−1.51,0.39)	0.25
18th month	33.73(4.05)	33.29(3.61)	−0.80(−1.78,0.19)	0.11
36th month	34.52(9.48)	33.87(10.28)	0	
Biochemical**				
Glucose				
Baseline	6.01(2.04)	6.13(2.13)	−0.14(−0.50,0.22)	0.46
36th month	6.14(2.23)	6.31(2.34)	0	
Total cholesterol				
Baseline	5.24(1.06)	5.49(1.12)	0.03(−0.15,0.22)	0.75
36th month	5.21(1.20)	5.47(1.16)	0	
HDL cholesterol				
Baseline	1.44(0.35)	1.39(0.35)	0.02(−0.04,0.07)	0.59
36th month	1.43(0.37)	1.38(0.36)	0	
LDL cholesterol				
Baseline	3.18(1.00)	3.41(1.01)	0.08(−0.09,0.25)	0.37
36th month	3.10(1.11)	3.36(1.04)		

(*Continued*)

Table 4 (Continued).

Parameter	Herbal Supplement Intake		Coefficient for Time (95% CI)	p for Trend*
	Yes	No		
Triglyceride				
Baseline	1.39(0.59)	1.54(0.78)	−0.14(−0.27,-0.01)	0.03
36th month	1.53(0.73)	1.62(0.86)		

Notes: *p<0.05 for the longitudinal analysis between users and non-users of herbal supplements. The model is fully adjusted for covariates such as such as age, gender, education years, smoking status, calf circumference, hand grip strength, chair sit and reach test, digit span, MMSE, GDS, VRI and VRII. **For biochemical data, data were only available at baseline and 36th month for selected participants (1011 for baseline and 870 for 36th month).

Abbreviations: Ref, reference group; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; VRI, Visual Reproduction I; VRII, Visual Reproduction II; GDS, Geriatric Depression Scale; MUAC, mid-upper arm circumference; HDL, high density lipoprotein; LDL, low density lipoprotein.

migration, refusal to join and ill health. Another suggested method for reducing attrition rate is via postal questionnaire, however this is not feasible for individuals who were illiterate, and for those who were unable to be contacted. Besides that, most of the parameters included in this study such as cognitive, physical fitness and biochemical tests were not suitable to be conducted via self-completion format.

In the adjusted linear mixed model, longitudinal association showed that both users and non-users of vitamin, mineral or herbal supplementation showed improvement in most of the investigated parameters especially for cognitive and physical function. This is closely related to the influence of the practice effect. It is rather usual for longitudinal studies to have serial cognitive and physical assessments, however these repeated measurements may lead to bias due to familiarity of the participants with the test items.[27] Thus, despite having improvement, we must not conclude that dietary supplementations are effective in improving the investigated parameters. Further intervention studies are needed to prove the effectiveness of these supplements. It is unavoidable to have repeated testing in a longitudinal study focusing on cognitive aging and physical fitness. Several other longitudinal studies such as Alzheimer`s Disease Anti-Inflammatory Prevention Trial (ADAPT),[28] Gingko Evaluation of Memory Study (GEMS),[29] and the Prevention of Alzheimer`s Disease by Vitamin E and Selenium (PREADViSE)[30] reported having repeated cognitive assessment and some studies having follow-up as frequently as every 3 months.

Findings demonstrated that baseline dietary supplement intake does not influence improvement in cognitive function. This is in agreement with the findings from the 12-year Physician`s Health Study II (PHSII), a randomized, double-blind, placebo-controlled trial which found no significant differences in the routine consumption of multivitamin in slowing cognitive decline between the treatment and control group. The large sample size of this trial, long duration, and good adherence of the participants boosts the power of the PHSII study to identify the effect of multivitamin supplementation towards cognitive changes among well-nourished, cognitively normal older adults.[31] In addition, The Mineral and Vitamin Intervention Study (MAVIS) found no improvement in digit span and verbal fluency test after one year of multivitamin supplementation among older adults.[32] Hence, this proved that we cannot rule out the long-term benefit of dietary supplement intake, despite improvement in cognitive function score in our study.

Depressive symptoms score was significantly higher at the 18th month follow-up, but it was still within the normal range among supplement users and non-users. A recent longitudinal study portrayed robust finding of a 75% increase in the possibility of developing depression among vitamin D deficient older individuals. The mechanism involved include the ability of vitamin D to cause alterations in the central nervous system function by causing neuronal excitotoxicity, reducing oxidative stress and helping in the formation of specific protein and neurotransmitters.[33] Although vitamin deficiency contributed to depression, it is essential to know that depression among older adults is very common and has various etiological factors such as disturbance in sleep cycle, lower neurotransmitter levels, functional limitations, poor socioeconomic status, low diet quality, lack of social support or comorbidities such as stroke and cancer.[34,35] Thus, use of dietary supplements alone is not able to improve the score of GDS.

Meanwhile, most physical performance tests showed practice effect in both the supplement users and non-users which portrayed a lack of influence of supplement intake on the tests. A meta-analysis indicated that vitamin supplementation, especially vitamin D, did not improve readings of hand grip strength and time up and go test.[36] Ageing is accompanied with skeletal muscle atrophy, declining muscle strength and reduced maximal oxygen uptake which leads to physical inactivity. Being dependent on dietary supplements alone is unable to improve physical fitness of older adults. Regular physical activity and healthy food choices are vital elements for improving skeletal muscle mass.

Furthermore, anthropometry data showed decreased waist and hip circumference at the 36th month follow-up. Waist circumference is a more reliable measure for indicating adiposity in older adults as compared to body mass index (BMI) due to the aging related changes in body composition. Waist circumference which indicated visceral fat may reflect activation of pro-inflammatory cytokines which may stimulate muscle catabolism leading to reduction in muscle strength. Declining visceral adiposity in the current study indicated better health status regardless of dietary supplement intake.[37]

In addition, all the biochemical parameters except triglyceride were not significant between users and non-users of dietary supplementation. This can be attributed to the presence of comorbidities or unhealthy dietary patterns which mostly consists of high saturated fat, cholesterol and sugar. Older adults are highly dependent on dietary supplements for lowering biochemical values and improving health status. A local study has found that most dietary supplement users were older adults with chronic diseases who use dietary supplements without the knowledge of their health professionals. Due to the influence of advertisement, there is a rise in the use of dietary supplements which heightens the risk of polypharmacy and drug-nutrient interaction.[38]

Natural dietary sources were the best and the safest strategy to nourish older adults. The World Health Organization (WHO) Report on Cognitive Decline and Dementia Risk Reduction indicated that a healthy diet consisting of fruits, vegetables, legumes, nuts and whole grains may reduce risk of cognitive impairment among older individuals. Moreover, this report demonstrated that dietary supplementation consumption may either have no effect or may lead to undesirable adverse health events due to higher dosage.[39]

This study has several strengths, namely the large number of participants covering a wide geographical area. Longitudinal analysis enables establishing an etiological relationship between intakes of dietary supplements with the investigated parameters. However, the limitation of this observational study is the use of self-reported data, especially in assessing intake of dietary supplementations. Future study must ask the subjects to bring along their supplement bottles or tag for reducing the possibility of recall bias. Data on physical activity level and dietary intake of the respondents were not included in this study. Moreover, the presence of practice effect may consequently bias the results of this study. Thus, future study must take appropriate steps to reduce the practice effects such as using different assessment tools for follow-up studies.

In conclusion, the results of the longitudinal study clearly demonstrated that there was improvement in cognitive function, physical fitness and anthropometric parameters regardless of dietary supplement usage at baseline. There is a need for a health policy to regulate the use of dietary supplementation in Malaysia. Older individuals must be educated on taking supplements with the advice of a physician. It is the role of the health professional to ensure that their client consumes supplements registered and licensed under the National Pharmaceutical Control Bureau, Malaysia (NPCB). Future studies should explore the effects of dietary supplementation in inducing genetic changes and brain atrophy.

Data Sharing Statement

The data is available upon request from the corresponding author, who can be contacted using the details given in the title page.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest.

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