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Intake of B vitamins and impairment in physical function in older adults☆

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SUMMARY

Background: The effect of vitamin B intake on physical function is not well known.
Objective: To examine the prospective association of the intake of vitamins B6, B12 and folate with physical function impairment in older adults.
Methods: We performed a prospective cohort study with 1630 participants from the Seniors-ENRICA study, a cohort of community-dwelling adults aged ≥60 years who were free of physical function impairment at baseline. In 2008–2010, nutrient intake was obtained through a validated computer-assisted face-to-face diet history. Study participants were followed-up through 2012 to assess incident impairment in agility and mobility, as well as impairment in overall physical functioning, defined as a decrease in the physical component summary of the 12-Item Short-Form Health Survey.
Results: Over a median follow-up of 3.5 years, we identified 343 individuals with agility limitation, 212 with mobility limitation, and 457 with decreased overall physical functioning. A significant association was observed between intake of vitamin B6 and lower risk of impaired mobility (odds ratio [OR] for highest vs. lowest tertile: 0.66; 95% confidence interval [CI]:0.44–0.99; p-trend = 0.05). The results lost significance when additionally adjusted for vitamin B12 and folate, however the OR did not materially change. A higher consumption of important sources of vitamin B6, such as fish or fruit, was also related to a lower risk of impaired mobility (OR 100-g increase in fish: 0.50; 95% CI: 0.32–0.79; OR 100-g increase in fruit: 0.92; 95% CI: 0.84–1.01). No association was found between vitamin B12 and folate intake and physical function.
Conclusions: A higher intake of vitamin B6 and of several of its main sources, such as fish and fruit, was associated with lower risk of impaired mobility in Spanish older adults.

1. Introduction

The older population is increasing progressively worldwide [1]. Consequently, the number of persons with limitations in mental and physical functioning, which are strongly associated with age, will surely increase in the next decades [2]. This is important because functional impairment augments the risk of several adverse health and social outcomes, including mortality and nursing home admissions [3]. Several modifiable health behaviors, such as smoking, low physical activity, excessive waist circumference and obesity, have been recently associated with limitations in physical functioning [4,5]. In addition, intakes of certain nutrients (e.g., antioxidants) and foods (fruit, vegetables and dairy products)

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have been related to better physical functioning in the old age [5–7]. However, the effect of nutritional factors on physical performance and disability remains largely unknown.

Some research has focused on plasma homocysteine, an amino acid often found elevated in the elderly and a sensitive marker for folate and vitamin B-12 deficiency [8]. Elevated plasma homocysteine level has been associated with lower physical performance [9–14]. Furthermore, the B vitamins are required as cofactors or substrates for enzymes essential for cell function and play a role in mitochondrial functioning via which they might preserve physical function during aging [15]. Only a limited number of studies have directly addressed the association between B vitamin supplementation or plasma levels of B vitamins and different measures of physical functioning; most of them have obtained inconclusive results [12,13,16–18]. In one study low serum concentrations of vitamin B has been linked to subsequent disability over 3 years of follow-up in older women [19]. Lastly, to our knowledge, only one study has focused on dietary B vitamins intake, and it found an inverse relationship between intake and risk of disability in instrument activities of daily living during a 13-year follow-up of older women [20]. Therefore, no previous research has yet examined the prospective association of dietary vitamin B intake with components of physical function in the early stages of the disability process, when it is easier to reverse. Using dietary information on B vitamins intake rather than serum levels could facilitate translation of study results into dietary recommendations.

In this study we prospectively investigated the association between the intake of vitamin B6, vitamin B12 and folate and a battery of measurements of physical function, including agility, mobility and overall physical functioning, in older men and women from Spain.

2. Methods

2.1. Study design and participants

Data were taken from the Seniors-ENRICA cohort, whose methods have been reported elsewhere [21,22]. In brief, the cohort was derived from the ENRICA study, a survey conducted in 2008–2010 among 12,948 individuals representative of the non-institutionalized adult population of Spain. The study participants aged 60 years or older comprised the Seniors-ENRICA cohort; of note, this population did not reflect the national structure of the Spanish older population. At baseline, information on socio-demographic variables, lifestyle, health status and morbidity was collected through a phone interview. In two subsequent home visits, appropriately trained research staff collected dietary information, conducted a physical exam and obtained blood and urine samples. Participants were followed up through 2012, when a second wave of data collection was performed to update information collected at baseline. We were able to conduct the analyses with 1630 individuals. A diagram describing the flow of participants across the study is shown in Fig. 1. Study participants gave written informed consent. The study was approved by the Clinical Research Ethics Committee of the La Paz University Hospital in Madrid.

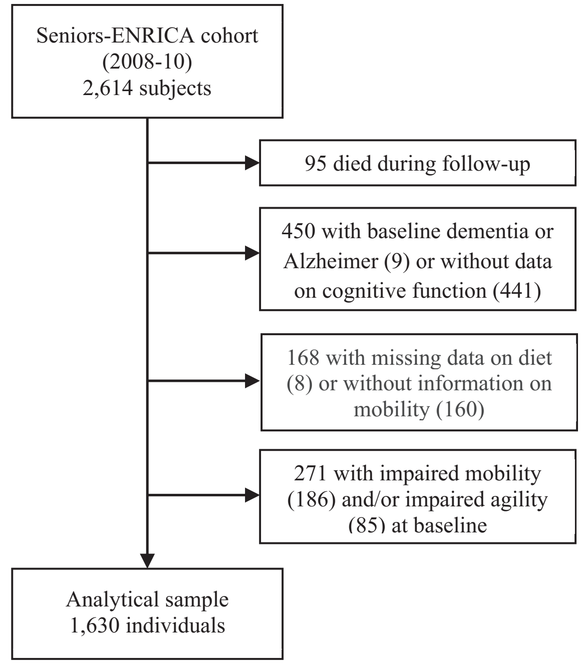

Fig. 1. Flow chart.

2.2. Study variables

2.2.1. Diet

At baseline, information on food consumption was obtained through a validated computer-assisted face-to-face diet history, which was developed from that used in the EPIC cohort study in Spain [23]. This instrument records the consumption of 880 foods in the preceding year, and includes a set of photographs to help in quantification of food portions. Vitamin B and other nutrient intakes were estimated using standard food composition tables [24–28]. The validity of the diet history was assessed against seven 24-h recalls over a one year period among 132 men and women. Pearson correlations were moderately good for vitamin B6 ($r = 0.50$), vitamin B12 ($r = 0.47$) and folate ($r = 0.46$) [23]. The use of vitamin B supplements has not been included due to the low use of vitamin B supplement in the cohort (<1%).

2.2.2. Physical function

We assessed three different domains of physical function: agility, mobility and overall physical functioning. Participants were defined as having impaired agility when they answered “a lot” to the following question from the Rosow and Breslau scale [29]: “On an average day with your current health, would you be limited in bending and kneeling?”, whose categories of response were “yes, a lot”, “yes, a little” and “not at all”. In the same way, impairment in mobility was defined as answering “a lot” to any of the following questions from the Rosow and Breslau scale: “On an average day with your current health, would you be limited in the following activities: 1) picking up or carrying a shopping bag?; 2) climbing one flight of stairs?; 3) walking several city blocks (a few hundred meters)?” Lastly, a limitation in overall physical function was deemed to exist when the score on the physical component summary of the 12-Item Short-Form Health Survey (SF-12) decreased ≥5 points from baseline to follow-up [30].

2.2.3. Other variables

At baseline, we obtained information on socio-demographic variables, lifestyle, anthropometrics and disease history. Educational level was classified into primary, secondary and university studies, and smoking status as never-, former-, and current-smoker. Weight and height were measured under standardized conditions. Body mass index (BMI) was calculated as weight (kg) divided by square height (m), and classified as <25, 25–29.9, and ≥30 kg/m^2. Physical activity during leisure time (metabolic equivalent hours/week) was ascertained with the EPIC-cohort questionnaire, validated in Spain [31]. Sedentary behavior was approximated by the time (hours/week) spent watching TV. Total energy intake (kcal/d) was estimated with standard composition tables of foods in Spain. Cognitive function was assessed with the Mini-Mental State Examination (MMSE), and cognitive decline was defined as a MMSE score of <23 [32]. Participants also reported the following physician-diagnosed diseases: osteomuscular disease, cardiovascular disease, cancer, chronic lung disease, and depression requiring treatment.

2.3. Statistical analysis

We used logistic regression to estimate the odds ratios (OR) and the 95% confidence interval (CI) of incident limitation in physical function according to intake of B vitamins. Intakes of B vitamins were first adjusted for total energy intake using the residuals method [33]. Next, participants were categorized into tertiles of vitamin B intake, and the first tertile (lowest intake) was used as the reference in the analyses. To investigate the dose–response relation, we modeled a 1 SD increase in vitamin B6 (0.5 mg), vitamin B12 (4 μg) and folate (100 μg) as a continuous variable.

Three logistic models were built: the first one adjusting for age and sex; a second model with additional adjustment for educational level, smoking status, ethanol intake, energy intake, BMI and further adjusting for diseases (osteomuscular disease, cardiovascular disease, cancer, chronic lung disease, depression requiring treatment and cognitive decline), to understand their impact on the studied association; the final model additionally adjusted for the other B vitamins that were not the exposure variable. For the models that included the change in overall physical functioning as the outcome, additional adjustment for the baseline value of the SF-12 physical component summary was performed.

We conducted several sensitivity analyses. First, we evaluated the role of physical activity and sedentary behavior in the studied associations by further adjusting the analyses for quintiles of time spent on leisure physical activity and/or hours/week of watching TV. Physical activity and sedentary behavior were not adjusted for in the main analysis to prevent over adjustment due to their close relation to the outcome. A possible modifying effect of sex was tested by using likelihood-ratio tests, which compared models with and without cross-product interaction terms. Given that we found no sex interactions, our results are presented for the total study sample. We have also assessed whether protein status influences our results by stratifying significant associations by protein intake. We furthermore replicated the analyses for important food sources of the B vitamins that were significantly associated with physical functioning. Finally, we estimated the risk associated with an intake below the Recommended Nutrient Intake (RNI) for vitamin B6 (M: 1.7; F: 1.5 mg/d), vitamin B12 (2.4 μg/d) and folate (400 μg/d) provided by the World Health Organization for older persons [34]. As well as the risk associated with an intake below the RNI for all three B vitamins.

Statistical significance was set at 2-tailed $p < 0.05$. Analyses were conducted using the SAS software, version 9.2 (SAS Institute Inc.). This manuscript followed the Strengthening the Reporting of Observational Studies in Epidemiology recommendations [35].

3. Results

Table 1 shows the characteristics of the study participants according to the tertiles of energy-corrected vitamin B6, vitamin B12 and folate intake. Compared to persons in the lowest tertile for each B vitamin, those in the highest tertile showed a higher intake of the other two B vitamins. The intake of vitamin B6 and folate was higher correlated (Pearson correlation coefficient = 0.61) than the intakes of vitamin B6 and B12 (Pearson correlation coefficient = 0.28) or vitamin B12 and folate (Pearson correlation coefficient = 0.03). Those with a higher vitamin B intake were significantly more often physically active and less often depressed. Participants with a higher vitamin B6 or folate intake were more often highly educated and were less often current smokers compared to those with a lower vitamin B6 intake. Furthermore, those in the highest tertile of vitamin B6 intake were significantly more often younger and showed less often sedentary behavior. Persons in the highest tertile of folate intake had significantly more often a BMI below 25.Over a median follow-up of 3.5 years, we identified 343 participants with incident impairment in agility, 212 with impaired mobility and 457 with a decline in overall physical function. We found a significant association between the intake of vitamin B6 and the risk of impaired agility in age- and sex adjusted analyses (OR for the highest vs. the lowest tertile: 0.72; 95% CI: 0.53–0.98; p-trend = 0.04) (Table 2). However this association was slightly attenuated and lost statistical significance when adjusted for the main confounders in model 2. In addition, we found no association between the intake of vitamin B12 or folate and impaired agility. By contrast, persons with a higher vitamin B6 intake were at lower risk of mobility limitation (model 2, OR for highest vs. lowest tertile: 0.66; 95% CI: 0.44–0.99; p-trend = 0.05) (Table 3). A 0.5 mg/day increase in vitamin B6 intake was associated with a 19% lower risk of impaired mobility. This result became borderline-significant when we additionally adjusted for vitamin B12 and folate, however the OR did not materially change. No evidence of an association between vitamin B12 and folate with impairment in mobility was found. Similarly, no association between B vitamins and decline in overall physical function was found (Table 4).

Additional adjustment of the main analyses for physical functioning and/or sedentary behavior did not modify the results (OR for highest vs. lowest tertile of B6 intake: 0.65; 95% CI: 0.40–1.07; p-trend = 0.10). Moreover, we observed a stronger association between a 0.5 mg/d increase in vitamin B6 intake and mobility among persons with a protein intake above the median (protein intake >90 g/d) (OR: 0.68, 95% CI: 0.49–0.94) (data not shown in tables).

We investigated main sources of vitamin B6 in the Spanish diet (meat, fish, vegetables, legumes, fruit and cereals) in association with risk of mobility limitation (Table 5). The contribution of each food source to the overall vitamin B6 intake was as follows: meat 22.47%, fish 12.17%, vegetables 13.45%, legumes 3.7%, fruit 14.59%, and cereals 11.28%. Meat showed to be the biggest contributor of vitamin B6 intake in our population. However, no significant association was found between meat and impairment in mobility. In the fully adjusted model, a 100-g increase in fish consumption was associated with lower risk of impaired mobility (OR: 0.50; 95% CI: 0.32–0.79). Persons with the highest fruit intake were also less likely to develop impaired mobility (OR highest vs. lowest tertile: 0.58; 95% CI: 0.39–0.87; p-trend = 0.01). Bananas and oranges were the main identified fruit sources of vitamin B6, bluefish was the main fish source of vitamin B6. Finally, we observed an increased risk of physical function impairment among those participants with intakes below the RNI for all vitamins (Supplemental Table 1).

4. Discussion

In this study, older adults with a higher intake of vitamin B6 had a lower risk of impairment in mobility. Also higher intakes of important vitamin B6 sources, such as fish and fruit, were associated with reduced incidence of mobility limitation. However, we did not find evidence of an association of vitamin B12 and folate with physical function.

Table 1
Population characteristics of the study participants across the tertiles of vitamin B intake (N = 1630).

	Vitamin B6			Vitamin B12			Folate		
	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
N participants	543	544	543	543	544	543	543	544	543
Intake B6, mg	1.5 ± 0.2	2.0 ± 0.1	2.6 ± 0.4*	1.9 ± 0.5	2.0 ± 0.4	2.2 ± 0.5*	1.7 ± 0.4	2.0 ± 0.4	2.4 ± 0.5*
Intake B6, mg, range	1.0–1.8	1.8–2.2	2.2–5.4	1.0–4.6	1.1–4.7	1.1–5.4	1.0–5.4	1.0–4.3	1.2–4.8
Intake B12, μg	5.4 ± 2.9	6.3 ± 3.2	7.4 ± 4.2*	3.6 ± 0.9	5.7 ± 0.6	9.7 ± 4.2*	6.2 ± 3.6	6.2 ± 2.9	6.7 ± 4.1*
Intake B12, μg, range	0.3–30.1	0.5–45.0	0.3–42.4	0.3–4.8	4.8–6.7	6.7–45.0	0.3–45.0	0.8–28.3	0.3–42.4
Intake folate, μg	257 ± 63	312 ± 72	381 ± 106*	317 ± 105	311 ± 87	322 ± 98	223 ± 37	304 ± 21	423 ± 78*
Intake folate, μg, range	11–531.5	149–646	143–1083	11–1083	103–737	83–793	11–270	270–343	343–1083
Age, y	69.6 ± 6.4	67.9 ± 5.8	67.7 ± 5.7*	68.4 ± 6.4	68.1 ± 5.8	67.7 ± 5.7	68.1 ± 6.1	68.1 ± 6.1	68.0 ± 5.7
Sex, men %	51.9	52.6	51.2	51.2	48.2	56.4	55.6	47.4	52.7
Educational level, %									
≤ Primary	54.3	50.7	45.5*	50.6	52.2	47.7	53.4	50.2	47.0*
Secondary	24.9	24.6	29.3	23.9	24.8	30.0	25.6	25.9	27.3
University	20.8	24.6	25.2	25.4	23.0	22.3	21.0	23.9	25.8
Smoking status, %									
Current smoker	16.4	12.1	9.0*	12.2	11.0	14.4	16.6	11.8	9.2*
Former smoker	28.0	34.0	33.7	32.0	30.9	32.8	31.3	29.6	34.8
Never smoker	55.6	53.9	57.3	55.8	58.1	52.9	52.1	58.6	56.0
Leisure-time physical activity, MET-h/week	21.4 ± 15.6	22.6 ± 14.7	24.4 ± 16.0*	21.7 ± 14.8	22.6 ± 15.8	24.1 ± 15.8*	21.1 ± 15.2	22.4 ± 15.3	24.9 ± 15.7*
Watching TV, h/wk	18.5 ± 11.7	17.2 ± 10.3	16.4 ± 10.2*	17.5 ± 11.1	17.3 ± 11.1	17.3 ± 10.1	17.7 ± 11.2	18.0 ± 10.9	16.5 ± 10.1
Energy intake, kcal/d	2117 ± 591	1991 ± 555	2067 ± 554	2163 ± 556	1966 ± 552	2046 ± 581	2106 ± 599	1977 ± 567	2092 ± 530
BMI, %									
<25	19.0	20.8	21.9	21.7	20.2	19.7	18.6	20.6	22.5*
25–29.9	54.1	51.1	50.8	51.8	52.4	51.9	48.4	55.5	52.1
≥30	26.9	28.1	27.3	26.5	27.4	28.4	33.0	23.9	25.4
Diagnosed diseases, %									
Cognitive decline [a]	2.4	2.0	1.8	1.7	2.0	2.6	1.7	2.9	1.7
Osteomuscular disease [b]	44.9	46.0	45.7	45.7	45.4	45.5	43.5	45.2	47.9
Cardiovascular disease [c]	4.4	5.2	5.3	4.4	5.2	5.3	4.8	4.8	5.3
Cancer	3.1	2.9	2.8	3.5	3.1	2.2	3.0	2.2	3.7
Chronic lung disease	9.4	9.6	8.5	8.5	9.9	9.0	9.2	8.5	9.8
Depression	9.6	6.1	4.8*	8.8	8.5	3.1*	8.3	7.2	5.0*

Abbreviations: BMI, Body Mass Index; Kcal, Kilocalories; MET, Metabolic equivalent; MMSE, Mini-Mental State Examination.
For continuous variables, mean and standard deviation are reported.
*Statistically different over the tertiles ($p < 0.05$).
[a] Cognitive decline is defined as a MMSE score <23.
[b] Osteo-arthritis, arthritis, and hip fracture.
[c] Ischemic heart disease, stroke, and heart failure.

Table 2
Odds ratios (95% confidence interval) for the association between vitamin B intake and impairment in agility during a 3.5 year follow-up of older adults (N = 1630).

	Tertile 1	Tertile 2	Tertile 3	P-trend	Continuous (per 1 SD)
N participants	543	544	543		
Vitamin B6					
Impairment in agility, n	127	121	95		343
Model 1	Reference	0.99 (0.74, 1.33)	0.72 (0.53, 0.98)	0.04	0.87 (0.76, 0.99)
Model 2	Reference	1.03 (0.74, 1.43)	0.78 (0.56, 1.11)	0.17	0.92 (0.80, 1.06)
Model 3	Reference	1.05 (0.74, 1.50)	0.79 (0.53, 1.18)	0.26	0.92 (0.77, 1.09)
Vitamin B12					
Impairment in agility, n	126	106	111		343
Model 1	Reference	0.77 (0.57, 1.05)	0.93 (0.69, 1.26)	0.62	0.93 (0.80, 1.08)
Model 2	Reference	0.67 (0.48, 0.93)	0.87 (0.62, 1.22)	0.41	0.91 (0.76, 1.08)
Model 3	Reference	0.68 (0.48, 0.95)	0.93 (0.65, 1.31)	0.63	0.93 (0.78, 1.12)
Folate					
Impairment in agility, n	119	119	105		343
Model 1	Reference	0.92 (0.69, 1.25)	0.84 (0.62, 1.14)	0.27	0.88 (0.77, 1.00)
Model 2	Reference	0.97 (0.70, 1.35)	0.91 (0.65, 1.28)	0.59	0.92 (0.79, 1.07)
Model 3	Reference	0.99 (0.70, 1.39)	1.01 (0.68, 1.48)	0.98	0.95 (0.80, 1.13)

Model 1: logistic model adjusted for age and sex.
Model 2: logistic model adjusted as in model 1 and for educational level (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), ethanol intake (quintiles of g/d), energy intake (quintiles of kcal/d), BMI (<25, 25–<30, ≥30 kg/m2), osteomuscular disease, cardiovascular disease, cancer, chronic lung disease, depression requiring treatment and cognitive decline.
Model 3: logistic model adjusted as in model 2 and for intakes of the other B-vitamins (tertiles of intake).

To our knowledge this is the first study that prospectively investigated the association between the dietary intake of vitamin B6, vitamin B12 and folate and self-reported physical functioning. The previous studies were very different in design and obtained somewhat inconclusive results. Among the longitudinal studies, in the INCHANTI cohort, with 698 participants, a low concentration of serum vitamin B6, vitamin B12 or folic acid was not associated with a loss of one point on the Short Physical Performance Battery score

Table 3
Odds ratios (95% confidence interval) for the association between vitamin B intake and impairment in mobility during a 3.5 year follow-up of older adults (N = 1630).

	Tertile 1	Tertile 2	Tertile 3	P-trend	Continuous (per 1 SD)
N participants	543	544	543		
Vitamin B6					
Impairment in mobility, n	82	78	52		212
Model 1	Reference	1.01 (0.71, 1.43)	0.63 (0.43, 0.92)	0.02	0.79 (0.67, 0.92)
Model 2	Reference	0.97 (0.66, 1.43)	0.66 (0.44, 0.99)	0.05	0.81 (0.67, 0.96)
Model 3	Reference	1.01 (0.67, 1.52)	0.69 (0.43, 1.13)	0.15	0.81 (0.65, 1.00)
Vitamin B12					
Impairment in mobility, n	76	75	61		212
Model 1	Reference	0.97 (0.68, 1.38)	0.86 (0.59, 1.24)	0.42	0.86 (0.70, 1.05)
Model 2	Reference	0.87 (0.59, 1.27)	0.81 (0.55, 1.22)	0.31	0.83 (0.66, 1.05)
Model 3	Reference	0.89 (0.61, 1.32)	0.90 (0.59, 1.37)	0.62	0.87 (0.69, 1.10)
Folate					
Impairment in mobility, n	78	71	63		212
Model 1	Reference	0.83 (0.58, 1.18)	0.78 (0.54, 1.12)	0.17	0.88 (0.75, 1.04)
Model 2	Reference	0.87 (0.59, 1.28)	0.79 (0.53, 1.18)	0.25	0.91 (0.76, 1.08)
Model 3	Reference	0.90 (0.60, 1.35)	0.94 (0.59, 1.48)	0.77	0.99 (0.80, 1.22)

Model 1: logistic model adjusted for age and sex.
Model 2: logistic model adjusted as in model 1 and for educational level (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), ethanol intake (quintiles of g/d), energy intake (quintiles of kcal/d), BMI (<25, 25−<30, ≥30 kg/m2), osteomuscular disease, cardiovascular disease, cancer, chronic lung disease, depression requiring treatment and cognitive decline.
Model 3: logistic model adjusted as in model 2 and for intakes of the other B-vitamins (tertiles of intake).

Table 4
Odds ratios (95% confidence interval) for the association between vitamin B intake and impairment in overall physical functioning [a] during a 3.5 year follow-up of older adults (N = 1630).

	Tertile 1	Tertile 2	Tertile 3	P-trend	Continuous (per 1 SD)
N participants	543	544	543		
Vitamin B6					
Impairment in overall physical functioning, n	168	148	141		457
Model 1	Reference	0.87 (0.66, 1.13)	0.79 (0.61, 1.04)	0.09	0.91 (0.81, 1.02)
Model 2	Reference	0.87 (0.66, 1.15)	0.82 (0.62, 1.09)	0.17	0.92 (0.82, 1.04)
Model 3	Reference	0.93 (0.69, 1.26)	0.98 (0.70, 1.37)	0.90	1.00 (0.87, 1.16)
Vitamin B12					
Impairment in overall physical functioning, n	153	166	138		457
Model 1	Reference	1.09 (0.83, 1.42)	0.87 (0.66, 1.14)	0.32	0.95 (0.83, 1.08)
Model 2	Reference	1.01 (0.77, 1.34)	0.83 (0.62, 1.11)	0.20	0.94 (0.82, 1.08)
Model 3	Reference	1.02 (0.77, 1.35)	0.84 (0.62, 1.13)	0.26	0.95 (0.82, 1.10)
Folate					
Impairment in overall physical functioning, n	158	166	133		457
Model 1	Reference	1.03 (0.79, 1.34)	0.78 (0.60, 1.03)	0.08	0.91 (0.81, 1.02)
Model 2	Reference	0.99 (0.75, 1.31)	0.76 (0.57, 1.02)	0.07	0.91 (0.80, 1.04)
Model 3	Reference	1.01 (0.75, 1.34)	0.77 (0.55, 1.08)	0.14	0.93 (0.80, 1.08)

Model 1: logistic model adjusted for age, sex and the SF-12 physical component summary at baseline.
Model 2: logistic model adjusted as in model 1 and for educational level (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), ethanol intake (quintiles of g/d), energy intake (quintiles of kcal/d), BMI (<25, 25−<30, ≥30 kg/m2), osteomuscular disease, cardiovascular disease, cancer, chronic lung disease, depression requiring treatment and cognitive decline.
Model 3: logistic model adjusted as in model 2 and for intakes of the other B-vitamins (tertiles of intake).
[a] ≥5-point decrease in the SF-12 physical component summary score from baseline to follow-up.

after 3-years of follow-up [17]. In addition, in the Longitudinal Aging Study Amsterdam, a weak association was found between low serum vitamin B12 and a decreased physical performance (combination of walking test, chair stand, and tandem stand) in the cross-sectional but not in the longitudinal analyses [13]. Finally, in a recent cross-sectional analyses of the Singapore Longitudinal Aging Study data, serum folate concentrations but not vitamin B12 concentrations were positively associated with balance but not with gait speed [12].

Intervention studies such as the B-PROOF study among 2919 elderly persons with elevated plasma homocysteine concentrations provided indications for a beneficial effect of an increased intake of vitamin B12 and folic acid on physical functioning [18]. Although the reduction in age-related decline in physical performance level and handgrip strength did not significantly differ between the intervention and control group during the 2 year follow-up because the supplementation of vitamin D in both treatment groups might have reduced the contrast between them, secondary analyses among compliant participants aged ≥80 years indicated that the intervention might have had a positive effect on walking performance. Another intervention study investigated the supplementation of vitamin B6, vitamin B12 and folic acid on movement performance measured by a postural-locomotor-manual test [16]. No benefit was found, which could be due to the short intervention period of 4 months and the small study size (n = 209).

A common consequence of impairment in physical functioning is disability, which can be defined as a difficulty or dependency in carrying out activities essential to independent living [36]. The only study that has also investigated dietary vitamin intake in association with disability showed that elderly women with a disability in instrumental activities of daily living presented a significantly lower dietary intake of vitamin B6 and B12 [20]. Moreover, in

Table 5
Odds ratios (95% confidence interval) for the association between sources of vitamin B6 intake and impairment in mobility during a 3.5 year follow-up of older adults (N = 1630).

	Tertile 1	Tertile 2	Tertile 3	P-trend	Continuous (per 100 g/d)
N participants	543	544	543		
Meat					
Mean intake (g/d)	54.37 ± 19.52	106.84 ± 14.92	191.17 ± 63.51		117.45 ± 68.69
Impairment in mobility, n	93	64	55		212
Multivariable model	Reference	0.79 (0.53, 1.16)	0.78 (0.51, 1.19)	0.22	0.80 (0.60, 1.06)
Fish					
Mean intake (g/d)	26.97 ± 12.00	59.46 ± 8.69	119.58 ± 92.66		68.66 ± 66.35
Impairment in mobility, n	94	66	52		212
Multivariable model	Reference	0.84 (0.57, 1.23)	0.67 (0.44, 1.02)	0.06	0.50 (0.32, 0.79)
Vegetables					
Mean intake (g/d)	90.21 ± 36.32	198.68 ± 32.60	381.71 ± 124.85		223.52 ± 143.01
Impairment in mobility, n	89	61	62		212
Multivariable model	Reference	0.80 (0.54, 1.19)	1.05 (0.69, 1.60)	0.89	0.94 (0.82, 1.07)
Legumes					
Mean intake (g/d)	15.12 ± 9.72	42.70 ± 8.47	117.52 ± 77.67		57.98 ± 62.67
Impairment in mobility, n	73	73	66		212
Multivariable model	Reference	1.14 (0.76, 1.69)	1.05 (0.69, 1.58)	0.82	1.05 (0.81, 1.37)
Fruit*					
Mean intake (g/d)	141.02 ± 63.63	300.09 ± 38.36	533.97 ± 147.91		325.01 ± 187.52
Impairment in mobility, n	83	70	59		212
Multivariable model	Reference	0.69 (0.47, 1.02)	0.58 (0.39, 0.87)	0.01	0.92 (0.84, 1.01)
Cereals					
Mean intake (g/d)	127.18 ± 40.66	223.96 ± 23.53	343.52 ± 77.76		231.55 ± 102.84
Impairment in mobility, n	82	70	60		212
Multivariable model	Reference	0.94 (0.62, 1.42)	1.04 (0.63, 1.69)	0.92	0.97 (0.80, 1.19)

Multivariable model: logistic model adjusted for age, sex, educational level (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), ethanol intake (quintiles of g/d), energy intake (quintiles of kcal/d), BMI (<25, 25–<30, ≥30 kg/m2), osteomuscular disease. Cardiovascular disease, cancer, chronic lung disease, depression requiring treatment, cognitive decline and the other food groups (in tertiles).
*Dried fruits and nuts are not included in this category.

another study low serum concentrations of vitamin B6 and B12 predicted a disability in activities of daily living 3 years later [19]. Our results provide new evidence of how higher intake of B vitamins may protect against the early stages of the disability process.

The association between B vitamins and physical function is thought to be mediated by the level of homocysteine. Elevated plasma homocysteine levels are related to lower muscle performance and physical limitations [14]. B vitamins play a role in the conversion of methionine to homocysteine. With removal of a methyl group by methionine, homocysteine is formed, which can then be methylated again through methionine synthase. Methionine synthase involves folate and vitamin B12 as a co-substrate and cofactor, respectively. Vitamin B6 is important as a cofactor in the trans-sulfuration of homocysteine into cysteine, which is one of the metabolic routes to prevent accumulation of homocysteine in the blood. Lastly, several mechanisms may explain the relation between homocysteine and physical function, including inflammation [37] and neurological problems [38,39].

The role of vitamin B6 in the amino acid metabolism makes the vitamin B6 requirement partly dependent on protein intake. In the older population, vitamin B6 status in plasma (pyridoxal-5-fosfate level) has been found to be higher among those that consumed a high vs. low protein diet [40]. We have assessed whether protein status has influenced our results by modeling the association between vitamin B6 and mobility stratified by protein intake and observed a greater benefit among persons with a dietary protein intake above the median. However, we cannot totally exclude that this might also be partly due to a beneficial impact of high protein intake on physical functioning.

Age affects the bioavailability of the B vitamins. This seems to be due to an underlying disease, such as atrophic gastritis, than to age itself [41]. The World Health Organization considers that the needs of B vitamins may be greater in the older adults and, thus, has defined RNI specifically for persons aged ≥51 [34]. Therefore, we investigated if participants with vitamin B intakes below the RNI had a lower risk of impaired physical functioning. The strong inverse association found for a deficiency in all B vitamins but not for individual deficiencies, suggests that clinically relevant short term effects require the accumulation of deficits.

We found that important sources of B vitamins, such as fish and fruits, were associated with a lower risk of impaired mobility. Meat contributed most to the vitamin B intake but was not associated with impairment in mobility. The overall effect of these food sources depend also on the other nutrients present in the foods. Fatty fish is rich in vitamin D that might improve musculoskeletal performance [42]. Also n-3 polyunsaturated fatty acids present in fish may be associated with physical function [43]. A large variety of vitamins and minerals are present in fruits, including anti-oxidants that might have influenced mobility through reducing oxidative stress [6].

Strengths of this study are its prospective design, the measurement of habitual food consumption with a validated diet history and adjustment for many potential confounders. Some limitations should also be acknowledged. We did not measure serum vitamin B or homocysteine levels; however, for nutritional recommendations, it seems appropriate to understand the association between dietary nutrient intake and health status. Also, we did not account for variations in vitamin B intake and other lifestyle changes that might have occurred during the follow-up, although it is presumable that long-term established habits, such as diet, have been maintained during the study period. Certain misreporting and misclassification of vitamin intake cannot be ruled out, despite excluding participants with an implausibly high or low energy intake level. Furthermore, some 'recency effect' might exist since recall of past food consumption may be distorted by current consumption [23]. The use of self-reported physical function may be less reliable than its objective measurement; however, reported function has been shown to predict early decline in performance

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and early disease [44]. Furthermore, because physical function includes different domains, we used several complementary definitions to capture all the complexity of this endpoint. Thus, the association of vitamin B6 with mobility but not with agility or overall physical function may reflect the differences of these definitions. Finally, as in any observational study, some residual confounding may persist.

5. Conclusions

A higher intake of vitamin B6 and of several of its main sources, such as fish and fruit, was associated with lower risk of impaired mobility in Spanish older adults. Given that Spain is one of the countries with a highest consumption of fish in the world, future research should confirm these results in populations with other sources of vitamin B, and in different settings (e.g., institutionalized individuals). In the meantime, promoting the consumption of healthy foods rich in vitamin B6 may be a safe and effective strategy to maintain physical function in the old age.

Authors' contributions

EAS, AL, PGC, FRA and ELG designed the research. EAS and ELG analyzed data. EAS and ELG wrote the manuscript. EAS, AL, PGC, FRA and ELG revised the manuscript for important intellectual content. ELG had primary responsibility for final content. All authors read and approved the final manuscript.

Conflict of interest

EA Struijk, Lana A, Guallar-Castillón P, Rodriguez-Artalejo F, Lopez-Garcia E, no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2017.05.016.

References

[1] United Nations, Department of Economic and Social Affairs, Population Division. World population prospects: the 2015 revision, key findings and advance tables. Working Paper No. ESA/P/WP.241.
[2] Prince MJ, Wu F, Guo Y, Robledo LMG, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. Lancet 2015;385(9967):549–62.
[3] Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49(2):M85–94.
[4] Guallar-Castillón P, Sagardui-Villamor J, Banegas JR, Graciani A, Fornés NS, López-Garcia E, et al. Waist circumference as a predictor of disability among older adults. Obesity 2007;15(1):233–44.
[5] Artaud F, Dugravot A, Sabia S, Singh-Manoux A, Tzourio C, Elbaz A, et al. Unhealthy behaviours and disability in older adults: Three-City Dijon cohort study. BMJ 2013;347:f4240.
[6] Cesari M, Pahor M, Bartali B, Cherubini A, Penninx BW, Williams GR, et al. Antioxidants and physical performance in elderly persons: the Invecchiare in Chianti (InCHIANTI) study. Am J Clin Nutr 2004;79(2):289–94.
[7] Houston DK, Stevens J, Cai J, Haines PS. Dairy, fruit, and vegetable intakes and functional limitations and disability in a biracial cohort: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr 2005;81(2):515–22.
[8] Jacques PF, Bostom AG, Wilson PW, Rich S, Rosenberg IH, Selhub J, et al. Determinants of plasma total homocysteine concentration in the Framingham Offspring cohort. Am J Clin Nutr 2001;73(3):613–21.
[9] Kado DM, Bucur A, Selhub J, Rowe JW, Seeman T. Homocysteine levels and decline in physical function: MacArthur studies of successful aging. Am J Med 2002;113(7):537–42.
[10] Kuo HK, Liao KC, Leveille SG, Bean JF, Yen CJ, Chen JH, et al. Relationship of homocysteine levels to quadriceps strength, gait speed, and late-life disability in older adults. J Gerontol A Biol Sci Med Sci 2007;62(4):434–9.
[11] Rolita L, Holtzer R, Wang C, Lipton RB, Derby CA, Verghese J, et al. Homocysteine and mobility in older adults. J Am Geriatr Soc 2010;58(3):545–50.
[12] Ng TP, Aung KC, Feng L, Scherer SC, Yap KB. Homocysteine, folate, vitamin B-12, and physical function in older adults: cross-sectional findings from the Singapore Longitudinal Ageing Study. Am J Clin Nutr 2012;96(6):1362–8.
[13] Van Schoor N, Swart K, Pluijm S, Visser M, Simsek S, Smulders Y, et al. Cross-sectional and longitudinal association between homocysteine, vitamin B12 and physical performance in older persons. Eur J Clin Nutr 2012;66(2):174–81.
[14] Swart K, Van Schoor N, Heymans M, Schaap L, Den Heijer M, Lips P, et al. Elevated homocysteine levels are associated with low muscle strength and functional limitations in older persons. J Nutr Health Aging 2013;17(6):578–84.
[15] Depeint F, Bruce WR, Shangari N, Mehtaa R, O'Briena PJ. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. Chem Biol Interact 2006 27;163(1–2):94–112.
[16] Lewerin C, Matousek M, Steen G, Johansson B, Steen B, Nilsson-Ehle H, et al. 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(5):1155–62.
[17] Bartali B, Frongillo EA, Guralnik JM, Stipanuk MH, Allore HG, Cherubini A, et al. Serum micronutrient concentrations and decline in physical function among older persons. JAMA 2008;299(3):308–15.
[18] Swart KM, Ham AC, van Wijngaarden JP, Enneman AW, van Dijk SC, Sohl E, et al. A randomized controlled trial to examine the effect of 2-year vitamin B12 and folic acid supplementation on physical performance, strength, and falling: additional findings from the B-PROOF study. Calcif Tissue Int 2016;98(1):18–27.
[19] Bartali B, Semba RD, Frongillo EA, Varadhan R, Ricks MO, Blaum CS, et al. Low micronutrient levels as a predictor of incident disability in older women. Arch Intern Med 2006;166(21):2335–40.
[20] Vercambre MN, Boutron-Ruault MC, Ritchie K, Clavel-Chapelon F, Berr C. Long-term association of food and nutrient intakes with cognitive and functional decline: a 13-year follow-up study of elderly French women. Br J Nutr 2009;102(03):419–27.
[21] Rodríguez-Artalejo F, Graciani A, Guallar-Castillón P, León-Muñoz LM, Zuluaga MC, López-García E, et al. Rationale and methods of the study on nutrition and cardiovascular risk in Spain (ENRICA). Rev Esp Cardiol 2011;64(10):876–82.
[22] León-Muñoz LM, García-Esquinas E, López-García E, Banegas JR, Rodríguez-Artalejo F. Major dietary patterns and risk of frailty in older adults: a prospective cohort study. BMC Med 2015;13(1):11.
[23] Guallar-Castillón P, Sagardui-Villamor J, Balboa-Castillo T, Sala-Vila A, Ariza Astolfi MJ, Sarrion Pelous MD, et al. Validity and reproducibility of a Spanish dietary history. PLoS One 2014;9(1):e86074.
[24] Farran A, Zamora R, Cervera P. Centre d'Ensenyament Superior de Nutrició i Dietética. Tablas de composición de alimentos. Barcelona: MCGraw-Hill/Interamericana de España, S.A.U. Edicions Universitat de Barcelona; 2004.
[25] Moreiras O, Carvajal A, Cabrera L, Cuadrado C. Tablas de composición de alimentos. 11ª Edición. Madrid: Ediciones Pirámide; 2007.
[26] Ortega Anta RM, López Sobaler AM, Carvalajes PA, Requejo Marcos AM, Molinero Casares LM. Programa DIAL. http://www.alceingenieria.net/nutricion.htm; 2007 [Accessed 12 April 2012].
[27] USDA, Agricultural Research Service. National nutrient database for standard reference. 2010. http://www.ars.usda.gov/Services/docs.htm?docid=8964 [Accessed 12 April 2012].
[28] Jiménez Cruz A, Cervera Ral P, Barcardí Gascón M. Tabla de composición de alimentos. 1ª Edición. Barcelona: Wander-Sandoz Nutrition; 1990.
[29] Rosow I, Breslau N. A Guttman health scale for the aged. J Gerontol 1966;21(4):556–9.
[30] Vilagut G, Valderas J, Ferrer M, Garin O, López-García E, Alonso J, et al. Interpretation of SF-36 and SF-12 questionnaires in Spain: physical and mental components. Med Clin 2008;130(19):726–35.
[31] Pols MA, Peeters PH, Ocke MC, Slimani N, Bueno-de-Mesquita HB, Collette H, et al. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. Int J Epidemiol 1997;26(Suppl 1):S181.
[32] Graciani A, Banegas JR, Guallar-Castillón P, Domínguez-Rojas V, Rodríguez-Artalejo F. Cognitive assessment of the non-demented elderly community dwellers in Spain. Dement Geriatr Cogn Disord 2006;21(2):104–12.
[33] Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65(4):1220S–8S.
[34] World Health Organization. Vitamin and mineral requirements in human nutrition. 2nd ed. http://www.who.int/nutrition/publications/micronutrients/9241546123/en/. [Accessed 11 January 2016].
[35] Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Prev Med 2007;45(4):247–51.
[36] Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59(3):M255–63.
[37] McDermott MM, Ferrucci L, Guralnik JM, Tian L, Green D, Liu K, et al. Elevated levels of inflammation, d-dimer, and homocysteine are associated with

adverse calf muscle characteristics and reduced calf strength in peripheral arterial disease. J Am Coll Cardiol 2007;50(9):897–905.

[38] Longstreth W, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people The Cardiovascular Health Study. Stroke 1996;27(8):1274–82.

[39] Soumaré A, Elbaz A, Ducros V, Tavernier B, Alpérovitch A, Tzourio C, et al. Cross-sectional association between homocysteine and motor function in the elderly. Neurology 2006;67(6):985–90.

[40] Pannemans DL, Van den Berg H, Westerterp KR. The influence of protein intake on vitamin B-6 metabolism differs in young and elderly humans. J Nutr 1994;124(8):1207–14.

[41] Russell RM. Factors in aging that effect the bioavailability of nutrients. J Nutr 2001;131(4):1359S–61S.

[42] Sharkey JR, Giuliani C, Haines PS, Branch LG, Busby-Whitehead J, Zohoori N, et al. Summary measure of dietary musculoskeletal nutrient (calcium, vitamin D, magnesium, and phosphorus) intakes is associated with lower-extremity physical performance in homebound elderly men and women. Am J Clin Nutr 2003;77(4):847–56.

[43] Reinders I, Murphy RA, Song X, Visser M, Cotch MF, Lang TF, et al. Polyunsaturated fatty acids in relation to incident mobility disability and decline in gait speed; the Age, Gene/Environment Susceptibility-Reykjavik Study. Eur J Clin Nutr 2015;69(4):489–93.

[44] Fried LP, Young Y, Rubin G, Bandeen-Roche K, Group WICR. Self-reported preclinical disability identifies older women with early declines in performance and early disease. J Clin Epidemiol 2001;54(9):889–901.

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