Age and Ageing 2018; **47:** 872–879
doi: 10.1093/ageing/afy105
Published electronically 25 July 2018

Low vitamin intake is associated with risk of frailty in older adults

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Abstract

Background: the association between vitamin intake and frailty has hardly been studied. The objective was to assess the association of dietary vitamin intake with incident frailty in older adults from Spain.
Methods: data came from a cohort of 1,643 community-dwelling individuals aged ≥65, recruited in 2008–10 and followed up prospectively throughout 2012. At baseline, 10 vitamins were assessed (vitamin A, thiamine, riboflavin, niacin, vitamins B6, B12, C, D, E and folates) using a validated face-to-face diet history. Incident frailty was identified using Fried's definition as having ≥3 of the following five criteria: unintentional weight loss of ≥4.5 kg, exhaustion, weakness, slow walking speed and low physical activity. Nonadherence to the recommended dietary allowances (RDA) was considered when the intake of a vitamin was below the recommendation. Analyses were performed with logistic regression and adjusted for main confounders.
Results: during a 3.5-year follow-up, 89 (5.4%) participants developed frailty. The odds ratios (95% confidence interval) of frailty for those in the lowest versus the highest tertile of vitamin intake were 2.80 (1.38–5.67), *P*-trend: 0.004, for vitamin B6; 1.65 (0.93–2.95), *P*-trend: 0.007, for vitamin C; 1.93 (0.99–3.83), *P*-trend: 0.06, for vitamin E and 2.34 (1.21–4.52), *P*-trend: 0.01, for folates. Nonadherence to the RDAs of vitamins was related to frailty for thiamine odds ratio (OR): 2.09 (1.03–4.23); niacin OR: 2.80 (1.46–5.38) and vitamin B6; 2.23 (1.30–3.83). When considering tertiles of RDAs for the 10 vitamins those who met <5 RDAs had a higher risk of frailty, OR: 2.84 (1.34–6.03); *P*-trend: <0.001, compared to those who met >7.
Conclusion: a lower intake of vitamins B6, C, E and folates was associated with a higher risk of frailty. Not meeting RDAs for vitamins was also strongly associated.

Keywords: *frailty, vitamin intake, older people, recommended dietary allowances, diet quality*

Introduction

Frailty is a geriatric syndrome that has sarcopenia as its pathophysiological basis. Age-related musculoskeletal changes and anorexia of ageing are also considered two main pathways for this syndrome. To be frail implies some degree of functional damage, and frail older adults experience a decrease in functional reserve and a lack of adequate response even to minor stressors (e.g. a cold, diarrhoea or dehydration). As a consequence, frail subjects have increased vulnerability to developing adverse health outcomes, including falls, disabilities and mortality [1–4]. Fried *et al.* [5] provided an operational definition to identify frailty that can be used to recognise frail older adults in clinical settings as well as for research purposes. Identifying frail older adults is of relevance because frailty is potentially reversible after being treated with physical activity and an appropriate diet [6].

There is evidence that poor nutrition is related to frailty [1, 7, 8], so, to some extent, frailty can also be considered as a nutrition-related condition [9]. Some physiological

changes occur in the gastrointestinal system with ageing (such as alterations in taste and smell, reduction of gastric motility and changes in gastrointestinal hormones). All these changes can modify dietary preferences, dietary intake and impair absorption of macro and micronutrients, leading to malnutrition and vitamin deficiencies. In addition, as we get older, poor adherence to a healthy diet can arise due to social reasons such as lack of access to fresh food or difficulties in handling and cooking of food. However, the longitudinal association of vitamin intake with incident frailty has hardly being studied among the elderly.

A cross-sectional analysis of the InCHIANTI Study assessed the association of vitamin intake with prevalent frailty. This analysis included individuals aged 65 and older and found that a low intake of vitamins D, E, C and folates was independently related to prevalent frailty [10]. Also, one longitudinal study, the Women's Health and Aging Study I (WHAS I), assessed the relationship of some serum vitamins with incident frailty among disabled women; a low concentration of carotenoids and vitamin E was associated with increased risk of frailty [11].

Therefore, vitamin intake and its association with frailty have not been prospectively and systematically studied in older adults, neither in men nor in women. Consequently, this study assessed the prospective association between both, dietary vitamin intake with incident frailty in older adults from Spain.

Methods

Study design and participants

Data were taken from the Seniors-ENRICA cohort, its methods have been previously reported [12–14]. Briefly, the cohort was established in 2008–10 with 2,519 individuals selected by stratified random sampling from the population aged 60 and older in Spain. At baseline, data were collected in three stages. Through a phone interview, we obtained information on sociodemographic variables, lifestyle, health status and morbidity, followed by a home visit to collect blood and urine samples; finally, a second home visit to carry out a physical examination and to collect dietary information. Participants were followed up throughout 2012, when a second wave of data collection was performed to update information on frailty.

For the current analysis, we excluded 372 individuals without baseline information on diet or with implausibly high or low energy intake (outside the range of 800–5,000 kcal/d for men or 500–4,000 kcal/d for women), plus 66 participants who were taking vitamin supplements. We also excluded 359 individuals with prevalent frailty or with limitations in instrumental activities of daily living measured with the Lawton and Brody scale. Of the remaining 1,722 participants, we additionally excluded 79 with missing values for confounders. Thus, the analyses were conducted with 1,643 individuals.

Study participants gave written informed consent. The study was approved by the Clinical Research Ethics Committee of *La Paz* University Hospital in Madrid.

Study variables

Vitamin intake

At baseline, information on food consumption was obtained using a validated face-to-face dietary history [15]. Participants were asked to indicate how frequently each specific food and beverage was habitually consumed in the preceding year. This instrument records the consumption of 880 foods, with a set of coloured photographs to help in the quantification of portions. Data on food consumption were converted into daily intake energy, macronutrients and micronutrients using standard food composition tables [16–19]. The intake of 10 *a priori* relevant vitamins below were assessed: vitamin A, thiamine, riboflavin, niacin, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E and folates. Participants were categorised into sex-specific tertiles for vitamin intake.

Nonadherence to the recommended dietary allowances (RDA) was considered when the intake of a vitamin was below the recommendation. To assess nonadherence to the RDAs, the Spanish recommendations for older population [16] were used: vitamin A μg/day: ≥1,000 in men or ≥800 in women; thiamine mg/day: ≥1 in men or ≥0.8 in women; riboflavin mg/day: ≥1.4 in men or ≥1.1 in women; niacin mg/day: ≥16 in men or ≥12 in women; vitamin B6 mg/day: ≥1.8 in men or ≥1.6 in women; vitamin B12 μg/day: ≥2 in men or women; vitamin C mg/day: ≥60 in men or women; vitamin D ≥ percentile 75 in men or women; vitamin E mg/day: ≥12 in men or women and folates μg/day: ≥400 in men or women. Those who met the corresponding RDA for the Spanish older population were used as reference.

Finally, by summing up the number of RDAs met for each participant, we obtained a score ranging from 0 to 10 that was classified in tertiles according to the number of recommendations met: <5, 5 to 7 and >7. Those who met >7 recommendations were used as reference.

Frailty

We used a minor modification of the operational definition of frailty developed by Fried and colleagues in the cardiovascular health study [5]. Specifically, frailty was defined as having three or more of the following five criteria: (i) weight loss, defined as unintentional loss of ≥4.5 kg of body weight in the preceding year; (ii) exhaustion was evaluated as a positive answer to either of the following two questions taken from the Centre for Epidemiologic Studies Depression Scale: 'Do you feel that anything you did was a big effort?' and 'Do you feel you could not keep on doing things?' at least 3–4 days a week; (iii) weakness, defined as the lowest quintile in the cardiovascular health study of maximum strength of the dominant hand, adjusted for sex and body mass index (BMI). Strength was measured using a Jamar dynamometer, and the highest value in two consecutive measurements was selected; (iv) slow walking speed, defined as the lowest cohort-specific quintile in our study sample for the three-metre walking speed test, adjusted for sex and height and (v) low physical activity, defined as walking ≤2.5 h/week in men and ≤2 h/week in women.

Other variables

At baseline, we obtained information on sociodemographic variables, anthropometrics, lifestyle and prevalent chronic diseases. Specifically, study participants reported their sex, age and educational level (primary, secondary and university). Weight and height were measured under standardised conditions. BMI was calculated as weight (kg) divided by height in metres squared. Participants also gave information on smoking status (never, former and current smoker). Sedentary behaviour was approximated by television viewing time (h/week). Total alcohol (g/day) and energy intake (kcal/d) were estimated with standard food composition tables from Spain [16–19]. They also reported whether they suffered from any of the following physician-diagnosed diseases: coronary heart disease, stroke, cancer, chronic pulmonary disease and type-2 diabetes mellitus.

Statistical analysis

The associations between tertiles of vitamin intake and incident frailty were summarised with ORs and their 95% confidence intervals (95% CI), obtained from multivariate logistic regression. The upper tertile of consumption was used as reference. Logistic models were adjusted for sex, age, educational level, BMI, smoking status, alcohol intake, television viewing time, total energy intake, coronary heart disease, stroke, cancer, chronic pulmonary disease and type-2 diabetes mellitus. Linear trend was assessed modelling the tertiles of vitamin intake as a continuous variable. Additionally, when in the logistic analysis, the *P* for trend was statistically significant, we also evaluated the dose–response relationship between vitamin intake and frailty by fitting nonparametric regression curves (cubic splines) adjusted for confounders. Other logistic models were built to assess the association between tertiles of the number of RDAs met at baseline and incident frailty.

Statistical significance was set at two-tailed $P < 0.05$. Analyses were conducted using the SAS software, version 9.4 (SAS Institute Inc.) and Stata/SE, version 11.1 (StataCorp, College Station, TX, USA).

Results

Over a mean follow-up time of 3.5 years, 89 (5.4%) participants developed frailty. Compared with nonfrail individuals those with frailty were more often women, and older, had a lower educational level and a higher BMI, spent more time watching TV and showed a higher frequency of coronary heart disease, stroke and diabetes. Also, they had lower intake of alcohol and of most vitamins (including vitamin A, thiamine, niacin, vitamins B6, B12, D, E and folates) (Table 1).

In fully adjusted analyses, the ORs (95% CI) of incident frailty for those in the lowest versus the upper tertile of vitamin intake were 2.80 (1.38–5.67) *P*-trend: 0.004 for vitamin B6, 1.93 (1.00–3.83) *P*-trend: 0.06 for vitamin E and 2.34 (1.21–4.52) *P*-trend: 0.01 for folates. The association was not statistically significant for the rest of vitamins, though the ORs were always above 1. For vitamin C intake, there was also a linear trend for the risk of frailty across tertiles ($P = 0.007$) (Table 2).

The achievement of RDAs for vitamins fluctuated between 22% for folates to 98% for vitamin B12. Nonadherence to the RDAs was related to frailty for thiamine (OR, 2.09; 95% CI, 1.03–4.23), niacin (2.80; 1.46–5.38) and vitamin B6 (2.23; 1.30–3.83) (Supplementary Table 1, available in *Age and Ageing* online). Furthermore, when comparing with those who met RDAs for >7 vitamins, those who met <5 vitamins had a higher risk of frailty (OR, 2.84; 95% [CI], 1.34 to 6.03) (Supplementary Table 2, available in *Age and Ageing* online).

When the dose–response association was depicted, the risk of frailty was linear for vitamin B6, C and E. However, for folates, the risk of frailty initially decreases when folate intake increases, down to a plateau around an intake of 350 mg/day (Figure 1).

Discussion

In the present analysis conducted with community-dwelling older adults, both poor intake of vitamins B6, C, E and folates and nonadherence to RDAs for thiamine, niacin and vitamin B6 were independently associated with incident frailty. Meeting a lower number of RDAs for vitamins was also strongly associated with a higher risk of frailty.

In a cross-sectional analysis conducted with 802 individuals aged 65 and over from the InCHIANTI study [10], low intake of vitamins D, E, C and folates was independently related to prevalent frailty. Our results are consistent with this study except for the fact that we did not find a significant association for vitamin D. Moreover, our findings are in line with other analysis from the InCHIANTI [20], showing that participants in the plasma highest vitamin E tertile were less likely to be frail than those participants in the lowest vitamin E tertile.

Only the WHAS I [11] study has previously analysed the association of some serum micronutrients and vitamins with incident frailty. In this analysis, conducted with 766 moderately to severely disabled community-dwelling older women, the risk of frailty was higher in those with low levels of carotenoids and vitamin E. We obtained similar results for vitamin E, but not for vitamin B6 or folates. Frail participants from the WHAS I study had higher serum concentrations of vitamin B6 and folates than nonfrail participants, however, the difference was not statistically significant. Vitamin C was not measured in the WHAS I study.

In our analyses, vitamin deficiencies were related to frailty, and the risk was higher in older people that met fewer number of RDAs for vitamins. This is in line with some previous studies reporting a relationship between better diet quality and lower risk of frailty [21, 22]. Thus, high diet quality was inversely associated with prevalent and incident frailty in older men [7], and also a diet that includes

Table 1. Baseline characteristics of the Seniors-ENRICA cohort study according to incident frailty status (N = 1,646).

Characteristics	Total (N = 1,646) Mean (SD) or n (%)	Not frail (n = 1,557) Mean (SD) or n (%)	Frail (n = 89) Mean (SD) or n (%)	P
Men	825 (50.1)	797 (51.2)	28 (31.5)	0.003
Age, years	68.1 (5.9)	67.8 (5.8)	72.2 (6.9)	<0.0001
Educational level				
Primary	863 (52.4)	793 (50.9)	70 (78.7)	<0.0001
Secondary	426 (25.9)	417 (26.8)	9 (10.1)	
University	357 (21.7)	347 (22.3)	10 (11.2)	
Body mass index (kg/m^2)	28.4 (4.2)	28.2 (4.1)	31 (5.2)	<0.0001
Smoking status				
Never smoker	934 (56.7)	876 (56.3)	58 (65.2)	0.095
Former smoker	509 (30.9)	483 (31.0)	26 (29.2)	
Current smoker	203 (12.3)	198 (12.7)	5 (5.6)	
Television viewing time (h/week)	17.4 (10.8)	17.1 (1.06)	22.3 (13.3)	<0.0001
Alcohol intake (g/day)	11.2 (18.4)	11.46 (18.6)	6.4 (14.6)	0.01
Total energy intake (kcal/day)	2,079 (745)	2,088 (750)	1,936 (629)	0.06
Prevalent diseases				
Coronary heart disease	22 (1.3)	18 (1.2)	4 (4.5)	0.007
Stroke	15 (0.9)	12 (0.8)	3 (3.4)	0.01
Cancer	27 (1.6)	25 (1.6)	2 (2.3)	0.64
Chronic obstructive pulmonary disease	115 (7.0)	105 (6.7)	10 (11.2)	0.11
Type-2 diabetes mellitus	235 (14.3)	213 (13.7)	22 (24.7)	0.004
Vitamin intake				
Vitamin A (μg/day)	869 (604.2)	874.7 (613.2)	775.5 (407.0)	0.13
Thiamine (mg/day)	1.4 (0.5)	1.4 (0.5)	1.3 (0.4)	0.04
Riboflavin (mg/day)	1.6 (0.5)	1.6 (0.5)	1.6 (0.6)	0.34
Niacin (mg/day)	21.1 (7.3)	21.2 (7.3)	19.3 (8.1)	0.02
Vitamin B6 (mg/day)	2.0 (0.6)	2.01 (0.6)	1.9 (0.6)	0.004
Vitamin B12 (μg/day)	6.4 (3.8)	6.4 (3.8)	5.3 (2.4)	0.006
Vitamin C (mg/day)	137.6 (70.7)	138.3 (70.7)	125.0 (70.0)	0.08
Vitamin D (μg/day)	3.4 (3.1)	3.5 (3.1)	2.8 (1.8)	0.03
Vitamin E (mg/day)	10.1 (5.1)	10.2 (5.1)	8.9 (3.8)	0.01
Folates (μg/day)	326.7 (112.6)	328.7 (112.5)	293.4 (111.1)	0.004

consumption of fruit, vegetables and dairy products has been associated with a lower risk of developing frailty in the short term [23, 24].

No data have been published on the association between meeting RDAs for vitamins and frailty. Our results suggest that deficiencies of several B vitamins are associated with frailty. Among them, deficiency for B6 might be considered the most important because it affected 30% of the sample. Moreover, although deficiencies for vitamin E and folates did not reach statistical significance when RDA cutoff points were considered, the intake of these vitamins is also of potential relevance because of their negative dose–response association with frailty when were classified in tertiles, and because the RDAs for those vitamins are not reached by the majority of the population; in our sample, less than 35% of the participants satisfied the RDAs for vitamins A, D, E and folates. Also, in the SENECA study, a considerable proportion of older adults had a deficiency in vitamin A, thiamine and riboflavin, despite an adequate nutritional status assessed by total energy intake and BMI [25].

Vitamins may play a role in the pathogenesis of frailty through several biological pathways. Most studies have focused on vitamin D and suggested that the relationship between vitamin D status and frailty is mediated by sarcopenia [26]. Scott *et al.* [27] have shown that 25-hydroxy-vitamin D increased muscle mass and strength over a 2-year follow-up. Furthermore, vitamin D stimulates muscle recovery, which is associated with an increase in muscle mass and strength in the elderly [28]. In cross-sectional studies, the association of serum 25-hydroxyvitamin D deficiency and frailty has been frequently observed [29–31]; but in prospective studies, circulating 25-hydroxy-vitamin D levels was weakly associated with frailty risk [32, 33]. Although vitamin D intake does not take into account the effect of sun exposure, our results are in line with a weak association.

Saum *et al.* [34] have reported a major role of oxidative stress and inflammation in the development of frailty. So, antioxidant vitamins such as vitamins A, C and E could play a role in frailty prevention. Also, Matteini *et al.* [35] found that vitamin B12 deficiency contributed to frailty in older women and they suggested that some genetic polymorphisms may lead to decreased vitamin B12 availability and contribute to the risk of frailty. Concerning vitamin B12, our results show a nonlinear negative association

Table 2. Odds ratios (95% interval, 95% CI) for the association between vitamin intake (tertiles) at baseline and incident frailty (N = 1,646).

Vitamins intake	Vitamin A		Thiamine		Riboflavin		Niacin		Vitamin B6	
	N/frail	OR (95% CI)	*N*/frail	OR (95% CI)	*N*/frail	OR (95% CI)	*N*/frail	OR (95% CI)	*N*/frail	OR (95% CI)
Tertile 1 (upper)	549/26	1.00 (Ref.)	549/27	1.00 (Ref.)	549/24	1.00 (Ref.)	549/24	1.00 (Ref.)	549/16	1.00 (Ref.)
Tertile 2	549/28	1.08 (0.62–1.90)	549/30	1.14 (0.63–2.07)	549/32	1.16 (0.66–2.07)	549/29	1.27 (0.71–2.28)	549/32	1.30 (0.75–2.25)
Tertile 3 (lower)	548/35	1.17 (0.64–2.15)	548/32	1.30 (0.68–2.51)	548/33	1.37 (0.73–2.61)	548/36	1.42 (0.73–2.77)	548/41	2.80 (1.38–5.67)**
P for trend		0.61		0.42		0.32		0.29		0.004
	Vitamin B12		**Vitamin C**		**Vitamin D**		**Vitamin E**		**Folates**	
	N/Frail	OR, (95% CI)	N/Frail	OR, (95% CI)	N/Frail	OR, (95% CI)	N/Frail	OR, (95% CI)	N/Frail	OR, (95% CI)
Tertile 1 (upper)	549/27	1.00 (Ref.)	549/23	1.00 (Ref.)	549/26	1.00 (Ref.)	549/21	1.00 (Ref.)	549/19	1.00 (Ref.)
Tertile 2	549/26	1.57 (0.89–2.79)	549/27	1.40 (0.82–2.41)	549/29	1.07 (0.61–1.86)	549/31	1.31 (0.75–2.30)	549/28	1.51 (0.87–2.63)
Tertile 3 (lower)	548/36	1.20 (0.66–2.17)	548/39	1.65 (0.93–2.95)	548/34	1.16 (0.66–2.05)	548/37	1.93 (0.99–3.83)*	548/42	2.34 (1.21–4.52)*
P for trend		0.48		0.007		0.61		0.06		0.01

*$P < 0.05$; **$P < 0.01$.

Model adjusted for sex, age (years), educational level (primary, secondary, university), body mass index (quartiles kg/m^2), smoking status (never smoker, former smoker, current smoker), alcohol intake (g/day), television viewing time (quartiles weekly hours), total energy consumption (quartiles kcal/day), coronary heart disease, stroke, cancer, chronic obstructive pulmonary disease and type-2 diabetes mellitus.

Tertiles cutoff points:

Vitamin A μg/day: 645; 1,054 in men and 571; 977 in women.

Thiamine mg/day: 1.2; 1.7 in men and 1.0; 1.5 in women.

Riboflavin mg/day: 1.5; 2.0 in men and 1.3; 1.8 in women.

Niacin mg/day: 19.6; 26.9 in men and 16.0; 22.9 in women.

Vitamin B6 mg/day: 1.9; 2.6 in men and 1.6; 2.2 in women.

Vitamin B12 μg/day: 4.9; 8.7 in men and 3.9; 6.9 in women.

Vitamin C mg/day: 98.1; 177.0 in men and 99.9; 179.9 in women.

Vitamin D μg/day: 2.1; 5.1 in men and 1.7; 4.2 in women.

Vitamin E mg/day: 8.2; 13.2 in men and 6.9; 11.7 in women.

Folates μg/day: 281.6; 415.9 in men and 254.0; 370.3 in women.

with the risk of frailty without achieving statistical significance.

In addition, all vitamins related to frailty in our analyses are considered essential, and each one could play a pathogenic role in frailty affecting muscle formation or maintenance. As such, vitamin B6 is related to the metabolism of amino acids; vitamin C is important in the formation of collagen; vitamin E is involved in the formation of muscles and other tissues and folates are involved in cellular division.

Our results are of public health relevance for several reasons. First, because the prevalence of frailty and its clinical importance are increasing even in developing countries [36]; Second, because nonadherence to RDA values for vitamins could warn us of the need for assessing frailty status. Lastly, because an inadequate nutritional intake is an important modifiable risk factor for frailty, it could be palliated by achieving the RDAs for B vitamins and increasing intake of some essential vitamins on a regular dietary basis.

Also, it is worth noticing that some clinical trials have found that taking daily multivitamins did not reduce major cardiovascular events, cancer outcomes and cardiovascular mortality [37–39]. However, the expected effects from vitamins in reducing mortality were much stronger in participants with vitamin insufficiency [40]. Our findings, however, were obtained with vitamins through the diet, and they do not endorse the use of pharmacological dose supplements that should only be used in the case of important deficiencies.

Finally, this study has several strengths such as being a longitudinal study of noninstitutionalised Spanish older adults. In addition, food consumption, specifically vitamin intake, was assessed with a validated computerised dietary history, that showed good correlation for nutrients and vitamins [15]. Also, many potential confounders were accounted for. Some limitations should also be acknowledged. We did not measure serum vitamin levels, as in many observational study, despite adjusting for many potential confounders, some residual confounding may persist. In the same way, between-person variability in vitamin intake cannot be ruled out as part of measurement errors.

In conclusion, in this prospective study, in older adults, poor vitamin intake for vitamin B6, C, E and folates and nonadherence to the RDAs were strongly and independently associated with frailty in the elderly. Both situations could be easily identified in clinical settings through a nutritional interview.

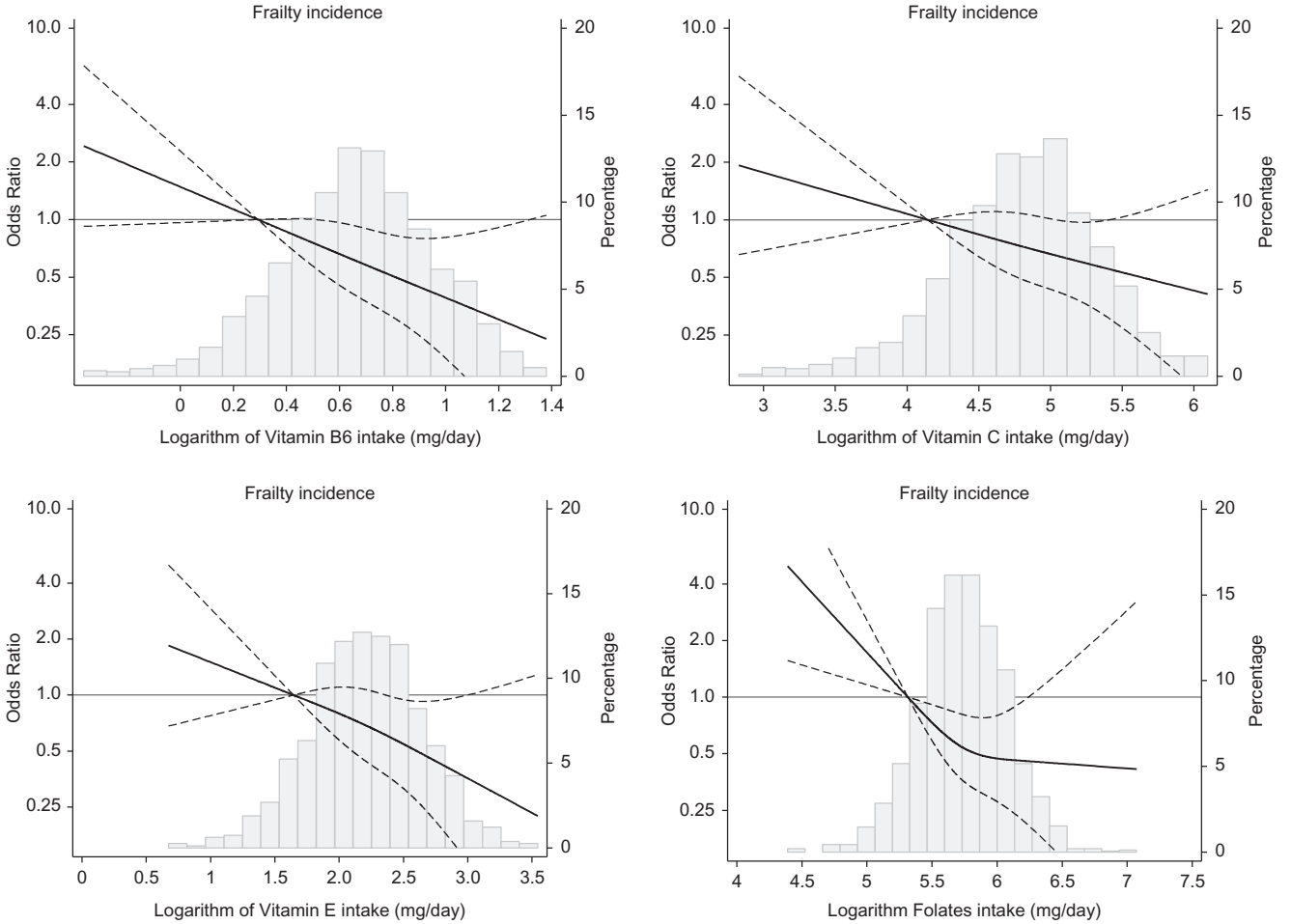

Figure 1. Dose–response association between vitamin intake and frailty (N = 1,646). Y-axis represents the OR for incident frailty and X-axis the logarithm of vitamin intake. Dashed lines are 95% confidence intervals. The bars represent the frequency of vitamin intake at baseline. Model adjusted for sex, age (years), educational level (primary, secondary, university), body mass index (quartiles kg/m^2), smoking status (never smoker, former smoker, current smoker), alcohol intake (g/day), television viewing time (quartiles weekly hours), total energy consumption (quartiles kcal/day), coronary heart disease, stroke, cancer, chronic obstructive pulmonary disease and type-2 diabetes mellitus.

Key points

- Poor vitamin intake and non-adherence to the RDAs for vitamins were strongly associated with frailty in the elderly.
- Low vitamin intake could be easily identified in clinical settings through a nutritional interview to prevent frailty in elderly.
- Deficiencies of several B vitamins are associated with frailty in elderly.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Authors' contributions

TBC and PGC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: TBC and PGC. Acquisition of data: PGC, FRA and ELG. Statistical analysis: TBC and PGC. Interpretation of data: TBC and PGC. Draughting of the manuscript: TBC and PGC. Critical revision of the manuscript for important intellectual content: EAS, ELG, JRB and FRA. Study supervision: PGC. All authors have read and approved the final manuscript.

Conflict of interest

None.

Funding

Data collection was funded by the following grants: FIS PI16/1512; PI16/1460; PI16/609; PI17/1709 (State Secretary of R+D and FEDER/FSE) Spanish Ministry of Economy and Competitiveness DEP2013-47786-R grant FEDER/FSE, the FRAILOMIC Initiative (EU FP7-HEALTH-2012-Proposal no. 305483-2), the ATHLOS project (EU H2020-Project ID: 635316), the SALAMANDER project (PCIN-2016-145) and the CIBERESP, Instituto de Salud Carlos III. Madrid, Spain.

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Received 15 January 2018; editorial decision 22 June 2018