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Original article

Cognitive function and vitamin B12 and D among community-dwelling elders: A cross-sectional study

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S U M M A R Y

Background & aims: Little is know on the association between mild or sub-clinical vitamin B12 or D deficiencies and cognitive decline. The objective of the present work was to evaluate the association between vitamin B12 and D levels, and cognitive function in community-dwelling elders.
Methods: Cross-sectional study that included data from elders who participated in the SABE study, a population-based study that was carried out in Ecuador. Participants of SABE were selected by probabilistic sampling from the whole country. Vitamin B12 and D were measured in blood and cognitive status was assessed using an abbreviated version of the minimental state examination (MMSE).
Results: The sample included 1733 elders from whom 936 (54.01%) were female. Independently from sex, age, years of education, ethnicity, socioeconomic status and geographical zone of residence, we found that vitamin B12 levels were associated to MMSE scores and that this relationship changed depending on age. In this way, we observed that from 75 years of age, drop of cognitive function was particularly steep in individuals with low levels of vitamin B12. We did not find evidence to support an association between vitamin D levels and cognitive function.
Conclusions: Low levels of vitamin B12 but not of vitamin D are associated with low cognitive functioning in a sample of community-dwelling elders.

1. Introduction

Cognitive abilities can be divided into domains, which include attention, memory, executive function, language and visuospatial abilities, among others. Each of these domains declines at different rates with age [1]. Specifically, studies in healthy elders show declines in task of attention, working memory and episodic memory in comparison to younger adults [2]. Moreover, age differences in brain activation during performance of cognitive tasks have been found in functional imaging studies [2]. Cognitive impairment is a major public health problem, as it is one of the leading causes of disability and adverse health consequences in elders [3]. Given the current lack of therapies for cognitive impairment, actual efforts are

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focused on identifying factors that may influence its development and progression [4].

Vitamin B12 also known as cobalamin, a water-soluble essential vitamin is one of the eight B vitamins. Vitamin B12 acts either as cofactor or coenzyme in a number of essential biochemical processes including DNA synthesis, cell metabolism and myelin maintenance [5]. In humans vitamin B12 is acquired from diet specially from meat, fish, shellfish and dairy products [5]. On the other hand, vitamin D is a fat-soluble secosteroid involved not only in calcium and phosphorus metabolism but also in genetic transcription via vitamin D receptors (VDR) [6,7]. Since few foods contain vitamin D (e.g., oil fish, egg yolk, shiitake mushrooms, liver or organ meats), dermal synthesis after ultraviolet B ray exposition remains the major route to obtain vitamin D [6].

During the last years, interest has risen around vitamins as key players in the prevention and treatment of cognitive decline [8,9]. In fact, associations between vitamin B12 or vitamin D and cognitive function in elders have been extensively investigated [10,11]. However, up to date evidence still does not support supplementation of vitamin B12 or vitamin D to prevent or treat cognitive decline [12,13]. In relation to normal aging, it is more likely that mild or sub-clinical vitamin deficiencies may play a role in cognitive decline rather than an overt vitamin deficiency [14]. Thus it is necessary to consider the status of vitamin B12 and vitamin D over a range of values and not just focus on deficiency when looking at cognitive outcomes [5]. The objective of the present work is to study the association of vitamin B12 and vitamin D levels and cognitive function in sample of community-dwelling elders.

2. Materials and methods

2.1. Study design and setting

The present work is the report of a cross-sectional study. Sample included elders who participated in the SABE study, formally know as "Salud, Bienestar y Envejecimiento" study, which was carried out by the "Ministerio de Inclusión Económica y Social" (MIES) and the "Instituto Nacional de Estadísticas y Censos" (INEC) in Ecuador between 2009 and 2012. The objective of SABE was to evaluate health status, well-being, nutrition, family, work, and cognition of elders in Ecuador [15]. Data and operational manuals of SABE are publicly available, and can be downloaded from INEC web page: https://anda.inec.gob.ec/anda/index.php/catalog/292.

2.2. Participants of SABE

Participants of SABE came from urban and rural areas of the Coast and Highlands of Ecuador. Participants were selected by stratified, double stage probabilistic sampling performed by clusters, so called domains (urban and rural areas) [15]. Strata refer to socioeconomic status (high, medium, low). During the first stage censal sectors were randomly selected from each domain. During the second stage dwellings were randomly selected form censal sectors, and finally all elders were selected from the dwellings. SABE was carried out in two phases: during the first one, health and epidemiological data were collected (SABE I). During the second phase a sub-sample of participants randomly selected from SABE I, underwent biochemical evaluation (SABE II) [15].

2.3. Eligibility criteria

Sample included all individuals from SABE II that is, all individuals who underwent biochemical evaluation (n = 2371). From them we randomly selected one individual from each dwelling (n = 1993) to assure independence of observations. We excluded individuals who did not have MMSE scores (n = 160), whose levels of vitamin D or B12 were not registered (n = 20) or whose sociodemographic data (e.g., age, ethnicity, years of education) were not available (n = 80). Thus, the final sample included 1733 male and female elders.

2.4. Variables

2.4.1. Cognitive function

Cognitive function was evaluated using an abbreviated version of the Mini Mental State Examination (MMSE), which produces an score that ranges from 0 to 19 [15,16]. The higher the MMSE score the better the level of cognitive function.

2.4.2. Vitamin B12

Levels of vitamin B12 in pg/ml in blood were measured by electrochemiluminescence (Immulite 2000 Roche) following international recommendations [15].

2.4.3. Vitamin D

Levels of vitamin D as 25(OH)D in ng/ml in blood were measured by chemiluminescence (Hitachi, Roche Cobas e 411) following international recommendations. The lowest limit of detection for serum 25(OH)D assay was 4 ng/ml [15].

2.4.4. Ethnicity

Ethnic group was determined by asking the participants: how do you identify yourself? Participants could identify themselves as "mestizo" (mixed ethnic ancestry), "indigena" (indigenous people), "blanco" (white) or another ethnic group (e.g., black, mulato, other) [15].

2.4.5. Socioeconomic status

Socioeconomic status was measured using an index that was developed applying principal component analysis. The index was constructed based on several variables including: health insurance and retirement, goods, housing quality, income and social subsidy [15]. The final variable includes 5 categories from 1 to 5. The lower the number the lower the socioeconomic status.

2.5. Statistical analysis

To investigate the association between MMSE scores (outcome) and vitamin B12 and D levels (exposures), we fit two linear regression models, one for vitamin B12 and another for vitamin D. MMSE scores as well as levels of vitamin B12 and D were analyzed as numerical variables. Each of the models was adjusted by sex [males, female], age in years, years of education, ethnicity [mestizo, indigenous, white, other], and place of residence [urban highlands, urban coast, rural highlands, rural coast]. Age and years of education were modeled as non-linear variables using restrictive cubic splines, where knot points were located at percentiles 5, 27.5, 50, 72.5, and 95, as previously recommended to avoid forcing curvature or inflections [17]. Models were also adjusted for sampling weights, which were extracted from SABE. Post-stratification weighting method was applied.

Restrictive cubic splines were also applied to vitamin B12 and D; however, neither vitamin B12 nor vitamin D showed non-linear trends (both $p > 0.05$), thus splines were removed. Because cognitive function normally declines with age, we included an interaction between vitamin B12 and age, and vitamin D and age to each the models. To explore whether vitamin B12 and vitamin D interacted, we fit a third model that an interaction term between vitamin B12 and D as categorical variables; however, there was not evidence of interaction (F (2) = 2.40, p = 0.090]). All statistical analyses were performed using R, RStudio and related packages available in R, including rms [17–19].

2.6. Ethical considerations

The study was conducted following ethical standards established in Helsinki Declaration 1964 [15]. Data of the study are publicly available and can be downloaded from the INEC web page.

2.7. Patient and public involvement statement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

3. Results

3.1. General characteristics of the sample

Final sample included 1733 elders, from whom 936 (54.01%) were female. Females and males had similar age. Females had had less years of education than males. Distribution of ethnic groups was similar among females and males, with mestizo being the most numerous group (Table 1). Distribution of SES shows that more than half of elders suffered from poverty and females were the most affected. Distribution of place of residence shows that more than half of elders lived in urban areas of the highlands and coastal region. Females more often reported living in the highlands and males in coast regions (Table 1).

Mean MMSE score for the sample was 14.50 (SD = 3.07), ranging from 4 to 19, with a median of 15. Mean vitamin B12 of the sample was 482.80 pg/ml, ranging from 149 to 1001, with median of 414. Mean vitamin D of the sample was 26.36 ng/ml, ranging from 3 to 71.17, with a median of 25.28. According to guidelines, in general sample showed normal levels of vitamin B12, while insufficient levels of vitamin D [20,21]. Still, 38.49% (n = 667) of the sample showed deficiency of vitamin B12, being males more often affected (Table 2). It was also observed that females showed lower median MMSE scores, as well as lower median levels of vitamin D than males. However, insufficiency and deficiency of vitamin D occurred more often among males (Tabla 2).

3.2. Vitamin B12 and vitamin D and cognitive function

We observed that vitamin B12 levels were statistically significantly associated to MMSE scores and that this relatioship changed depending on age [F [3] = 4.07, p = 0.007]. For elders older than 75 years of age, higher levels of vitamin B12 led to higher MMSE scores than low levels of vitamin B12 (Fig. 1, panel a; Supplementary Table 1). In contrast, for elders younger than 75 years of age, levels of vitamin B12 were not associated to MMSE scores (Fig. 1, panel a; Supplementary Table 1). On the other hand, there was not evidence of association between vitamin D levels and cognitive function (F [3] = 0.77, p = 0.509; Fig. 1, panel b). We also investigated whether the relation between vitamin B12 levels and MMSE scores depended on vitamin D levels that is, if MMSE scores were different among individuals with vitamin B12/D deficiency and those with normal vitamin B12/D levels. However, although MMSE scores were higher among individual with normal vitamin B12/D levels than among those with vitamin B12/D deficiency, that difference was not statistically significant (Supplementary Table 2).

3.3. Cognitive function and other covariates

Cognitive function was statistically significantly associated with age [$F(8) = 17.19, p < 0.001$], sex [$F(1) = 10.68, p = 0.001$], ethnicity [$F(3) = 15.83, p < 0.001$], years of education [$F(3) = 20.09, p < 0.001$], place of residence [$F(3) = 5.94, p = 0.001$], but not with socioeconomic status [$F(4) = 1.38, p = 0.240$]. In this way, cognitive function decreased with age, was lower in females in comparison to males, was lower in indigenous people in comparison to the other ethnic groups, was higher as years of education increased, was lower for elders residing in urban and rural highland regions in comparison to urban and rural coast regions. Adjusted means of MMSE scores for different covariates by sex are showed in Table 3.

4. Discussion

The objective of the present work was to study the association between cognitive function and levels of vitamin B12 and D in a population-based context. Independently from sex, age, years of education, ethnicity, socioeconomic status and place of residence, we found that vitamin B12 but not vitamin D was associated with cognitive function in a representative group of Ecuadorian elders. Elders with lower levels of vitamin B12 showed worse cognitive

Table 1
General characteristics of the sample. Sample included 1733 individuals. Abbreviations: IQR, interquartil range; n, number; %, percentage; SEE, socioeconomic status.

		Female 936 (54.01%)		Male 797 (45.99%)	
		Median (IQR)	n (%)	Median (IQR)	n (%)
Age		69 (64,76)		68 (64,76)	
Years of education		3 (0,6)		4 (2,6)	
Ethnicity	Mestizo		656 (70.09)		568 (71.27)
	Indigenous		71 (7.59)		62 (7.78)
	White		135 (14.42)		86 (10.79)
	Other		74 (7.91)		81 (10.16)
SES	1		281 (30.02)		235 (29.49)
	2		250 (26.71)		179 (22.46)
	3		144 (15.38)		169 (21.2)
	4		201 (21.47)		126 (15.81)
	5		60 (6.41)		88 (11.04)
Region	Urban highlands		282 (30.13)		209 (26.22)
	Urban coast		367 (39.21)		285 (35.76)
	Rural highlands		188 (20.09)		164 (20.58)
	Rural coast		99 (10.58)		139 (17.44)

Table 2
MMSE, vitamin B12 and vitamin D by sex. Abbreviations: IQR, interquartil range; MMSE, mini mental state examination.

		Female		Male	
		Median (IQR)	n (%)	Median (IQR)	n (%)
MMSE		14 (12,16)		15 (13,17)	
Vitamin B12 (pg/ml)		480 (313.75, 718.25)		360 (243, 539)	
	Normal (>350)		650 (69.44)		416 (52.20)
	Deficiency (≤350)		286 (30.56)		381 (47.80)
Vitamin D (ng/ml)		22.91 (18.29, 27.97)		28 (23.02, 33.82)	
	Normal (>30)		322 (37.53)		107 (14.40)
	Insufficiency (21–29)		362 (42.19)		312 (42.00)
	Deficiency (<20)		174 (20.28)		324 (43.60)

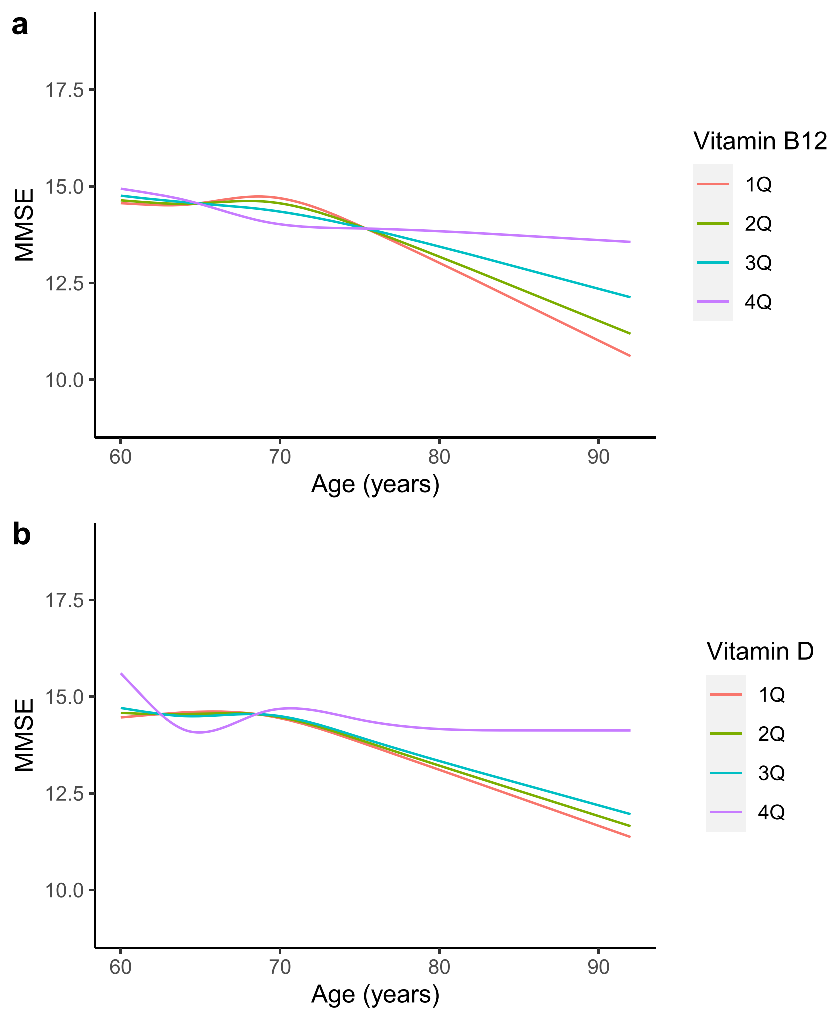

Fig. 1. Vitamin B12, D and cognitive function by age. Panel a shows adjusted predicted mean MMSE scores for the first (271 pg/ml), second (414 pg/ml)), third (647 pg/ml), and fourth (1001 pg/ml)) quartile of vitamin B12. Panel b shows adjusted predicted MMSE scores for the first (20.07 ng/ml), second (25.28 71.17 ng/ml), third (31.04 71.17 ng/ml) and forth quartil (71.17 ng/ml) of vitamin D. Abbreviations: MMSE, Mini-Mental state examination; 1st Q, first quartile; 2nd Q, second quartile; 3rd Q, third quartile; 4th Q, forth quartile.

function that is, lower scores in the MMSE. Interestingly, the drop of cognitive function was particularly steep when elders were 75 years old or older.

4.1. Vitamin B12 and D status among Ecuadorian elders

When compared to reference values, median levels of vitamin B12 were normal, not so those of vitamin D, which were lower in our sample (see Table 2). Still, 38.49% of elders showed vitamin B12 deficiency. Owing the high prevalence of atrophic gastritis among elders in comparison to the younger population, vitamin B12 deficiency may result from decreased absorption of protein-bound vitamin B12 [22]. Atrophic gastritis may also induce reduced release of free vitamin B12 from food proteins and often result in excess of bacteria that consume nutrients including vitamin B12 [22].

Although atrophic gastritis is a known risk factor of low vitamin B12 status, a deficiency of this vitamin might be also find in

Table 3
Adjusted predicted means for MMSE scores. Sample included 1733 individuals. Abbreviations: M, mean; LCI, lower confidence interval; UCI, upper confidence interval; SEE, socioeconomic status.

		Female			Male		
		M	LCI	UCI	M	LCI	UCI
Age (years)	60	14.64	14.11	15.17	15.06	14.53	15.60
	70	14.56	14.11	15.01	14.99	14.54	15.44
	80	13.18	12.74	13.63	13.61	13.18	14.03
	90	11.52	10.81	12.23	11.95	11.23	12.66
Education (years)	0	12.86	12.41	13.31	13.29	12.80	13.77
	6	15.59	15.15	16.04	16.02	15.57	16.47
	12	16.29	15.72	16.85	16.71	16.14	17.29
	18	16.50	15.61	17.40	16.93	16.03	17.83
Ethnic group	Mestizo	14.61	14.17	15.05	15.03	14.59	15.48
	Indigenous	13.16	12.50	13.81	13.59	12.93	14.24
	White	13.94	13.41	14.46	14.36	13.83	14.90
	Other	13.96	13.39	14.53	14.39	13.82	14.96
SES	1	14.61	14.17	15.05	15.03	14.59	15.48
	2	14.55	14.04	15.06	14.97	14.46	15.49
	3	14.83	14.33	15.33	15.26	14.76	15.75
	4	14.91	14.42	15.41	15.34	14.84	15.84
	5	15.23	14.51	15.96	15.66	14.94	16.38
Region	Urban highlands	14.16	13.70	14.62	14.58	14.11	15.06
	Urban coast	14.61	14.17	15.05	15.03	14.59	15.48
	Rural highlands	14.16	13.67	14.65	14.58	14.10	15.07
	Rural coast	14.91	14.40	15.42	15.33	14.84	15.83

populations with low prevalence of atrophic gastritis [23]. In such populations vitamin B12 deficiency is usually related to low intake of vitamin B12-rich foods, notably animal source foods [24]. Typically diets of vulnerable groups (e.g., elders) from populations in low/medium income countries like Ecuador, are low in animal source food because of their relative high cost and lack of availability [24–26]. Other causes of vitamin B12 deficiency among elders may include consumption of medication such as metformin, omeprazole, etc. [22,27].

Regarding vitamin D, we found that 68.89% of elders showed vitamin D deficiency or insufficiency. Since Ecuador receives sunlight all year around, and ultraviolet radiation is necessary for vitamin D synthesis, it was striking to find such a high prevalence of vitamin D insufficiency or deficiency among elders. Still, similar percentages of vitamin D deficiency or insufficiency have been reported in elders from Argentine and Brazil [28,29]. Worldwide the prevalence of vitamin D deficiency or insufficiency ranges between extreme values and there is evidence of age-related differences [30].

Vitamin D insufficiency or deficiency among Ecuadorian elders might be explained by a lower exposition to ultraviolet radiation because of the combination of dark skin pigmentation, clouds cover and wearing wool clothes to protect from cold climates, especially at high altitudes [31,32]. In fact, a high prevalence of vitamin D deficiency has been observed among older indigenous of Ecuador, who live at high altitude regions including, Chimborazo, Cotopaxi, Imbabura and Bolivar [32]. Vitamin D insufficiency and deficiency may also arise from a poor daily intake of vitamin D in the diet [26].

4.2. Vitamin B12 and cognitive function

Our results are in line with those of previous studies which suggest a connection between low levels of vitamin B12 or high levels of homocysteine (a by product of vitamin B metabolism) and impaired cognitive ability [9,33]. A similar association has been described in Parkinson disease patients with cognitive dysfunction, who are more likely to have higher homocysteine levels as well as lower folate and vitamin B12 levels than patients with normal cognitive function [34]. In contrast, evidence in community-dwelling elders indicate that neither vitamin B12, nor vitamin B6 or folate are associated dementia risk [35]. Furthermore, there is only limited evidence that support the use of vitamin B12 or other vitamin or mineral supplementation to prevent, delay or treat cognitive impairment or dementia [36–39].

4.3. Vitamin D and cognitive function

We did not found evidence of a relationship between vitamin D levels and cognitive function. Our results are in agreement with those of a Mendelian randomization study that found no evidence of a causal association between serum vitamin D levels and cognitive performance [13]. In contrast, the findings of a meta-analysis suggest that low vitamin D levels are related to poorer cognition [10]. Such conflicting results are probably explained by the fact that low levels of vitamin D are associated with a number of chronic conditions that can precipitate the progression of cognitive decline and likely introduce bias to observational studies [13,40].

4.4. Implications, strengths and limitations

Available evidence from randomized controlled trials, which show no obvious cognitive benefit from the use of B12 vitamin supplements, can not be taken as definitive, as most of them tend to be too short as to evidence changes in cognitive function. Moreover, it seems that once vitamin B12 deficiency is established, damage in cognitive function can not longer be treated or reversed as changes that predispose to cognitive decline probably start early in life [41,42]. Future studies including diverse populations are needed to assess whether in the long-term low levels of vitamin B12 (in the absence of manifested deficiency) have a role in the progression of cognitive decline [43].

In Ecuador, as far as we know, a similar study has not been carried out and therefore, ours opens channels of discussion on the role of vitamin B12 and D on cognitive decline among elders. Moreover, since participants were selected by probabilistic sampling, our findings are generalizable to the Ecuadorian population. However, our study has also various limitations: 1) Due to the current design and data we were not able to establish a causal association between vitamin B12 levels and cognitive function. 2) Although cognitive function was evaluated by trained personnel using a previously validated test, there is still risk of lack of precision. 3) Despite we adjusted our models by influential confounders (e.g., age and years of education), we were not able to take into account the impact of other factors including previous comorbidities or use of medication.

5. Conclusions

Low levels of vitamin B12 but not of vitamin D are associated with low cognitive functioning in a sample of community-dwelling older adults. Levels of vitamin B12 interacted with age in a non-linear fashion.

Founding

None.

Author contributions

The main author of this work declares that all authors have contributed and work on the development of it as follows. AFVV: Conception and design, analysis and interpretation of data, drafting of the article, final approval of the version to be published. TVCA: Conception and design, analysis and interpretation of data, drafting of the article, final approval of the version to be published. JSVM Conception and design, analysis and interpretation of data, drafting of the article, final approval of the version to be published. ECTV: Critical revision for important intellectual content, writing and final approval of the version to be published. JSPA: Critical revision for important intellectual content, writing and final approval of the version to be published. TMNC: Critical revision for important intellectual content, writing and final approval of the version to be published. SIHA: Critical revision for important intellectual content, writing and final approval of the version to be published. MFVV: Conception and design, analysis and interpretation of data, drafting of the article, critical revision for important intellectual content, final approval of the version to be published.

Data statement

Data and operational manuals of SABE are publicly available and can be downloaded from INEC web page: Data and operational manuals of SABE are publicly available and can be downloaded from INEC web page: https://anda.inec.gob.ec/anda/index.php/catalog/292.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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