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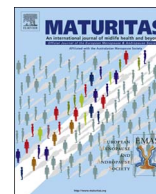
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# Association of hypovitaminosis D with triceps brachii muscle fatigability among older women: Findings from the EPIDOS cohort

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## ABSTRACT

**Background:** Vitamin D affects physical performance in older adults. Its effects on muscles, notably on muscle strength, remain unclear. The objective of this cross-sectional study was to determine whether hypovitaminosis D is associated with triceps brachii muscle fatigability in community-dwelling older women.

**Methods:** A randomized subset of 744 women aged  $\geq 75$  years from the EPIDOS cohort was categorized into two groups according to triceps brachii muscle fatigability, defined as loss of strength  $> 5\%$  between two consecutive maximal isometric voluntary contractions. Hypovitaminosis D was defined using consensual threshold values (i.e., serum 25-hydroxyvitamin D concentration [25OHD]  $\leq 10$  ng/mL,  $\leq 20$  ng/mL, and  $\leq 30$  ng/mL). Age, body mass index, comorbidities, use psychoactive drugs, physical activity, first triceps strength measure, hyperparathyroidism, serum concentrations of calcium, albumin and creatinine, season and study centers were used as potential confounders.

**Results:** The prevalence of hypovitaminosis D  $\leq 30$  ng/mL was greater among women with muscle fatigability compared with the others ( $P = .009$ ). There was no between-group difference using the other definitions of hypovitaminosis D. The serum 25OHD concentration was inversely associated with the between-test change in triceps strength (adjusted  $\beta = -0.09$  N,  $P = .04$ ). Hypovitaminosis D  $\leq 30$  ng/mL was positively associated with triceps fatigability (adjusted OR = 3.15,  $P = .02$ ).

**Conclusions:** Vitamin D concentration was inversely associated with the ability to maintain strength over time in this cohort of community-dwelling older women. This is a relevant new orientation of research toward understanding the involvement of vitamin D in muscle function.

## 1. Introduction

Lower concentrations of 25-hydroxyvitamin D (25OHD) are very common in elderly population living in institutions or in the community, reaching up to 90% of older adults [1]. The clinical relevance is that hypovitaminosis D is accompanied by adverse health events. For instance, hypovitaminosis D is associated with poorer physical

performance in older adults [2,3]. The explanation most commonly offered is based on the possible involvement of vitamin D in muscle health and function [3], as suggested by experimentation reporting the presence of vitamin D receptors (VDRs) in muscle cells [4]. However, it is noticeable that previous clinical studies on hypovitaminosis D and muscle strength have shown conflicting results [5]. Some cross-sectional studies reported decreased muscle strength in the case of

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hypovitaminosis D [6,7], although others did not find any significant association [8,9]. Moreover, a meta-analysis of interventional trials showed that vitamin D supplementation could not enhance muscle strength after 9 months of supplementation on average [5]. The latter result weakened the plausibility of a link between vitamin D and muscle strength, and strengthened the assumption that vitamin D may impact muscles in a different way.

Muscle strength is inversely related to fatigue [10]. Mechanistically, while the strength depends on the mass of striated muscles, the fatigability (i.e., the muscle ability to continue effort and maintain constant work over time) depends mainly on muscle mitochondrial function. Mitochondrial cofactors enhance the synthesis of ATP, act as a powerful anti-radical, and reduce the level of lactic acid thereby decreasing muscle fatigue [11]. Interestingly, recent findings suggest that vitamin D is involved in mitochondrial oxidative function in skeletal muscles [12]. Specifically, Sinha et al. reported that the energy production during the recovery phase of modest exercise by muscle mitochondria is impaired among people with hypovitaminosis D [12]. Thus, as mitochondrial oxidative phosphorylation is the primary source of cellular ATP, itself source of energy for the myosin-adenosin system in the striated muscle, the suboptimal mitochondrial function accompanying hypovitaminosis D may lead to greater fatigability [12].

We hypothesized that vitamin D status could influence muscle fatigability in older adults. We had the opportunity to examine the association of serum 25OHD concentration with muscle fatigability in a randomized sample of healthy women aged 75 years and older from the large representative community-based EPIDémiologie de l'OStéoporose (EPIDOS) cohort. The objective of the present cross-sectional analysis was to determine whether hypovitaminosis D was associated with triceps brachii muscle fatigability in older women.

## 2. Methods

### 2.1. Participants

We studied 744 older women, a randomized subset of the EPIDOS study, a French observational prospective multicentric national cohort designed to evaluate the risk factors for hip fracture among community-dwelling older women. Sampling and data collection procedures have been described in detail elsewhere [13]. In summary, from 1992 to 1994, 7598 women aged 75 years and older were recruited from electoral lists in five French cities (Amiens, Lyon, Montpellier, Paris and Toulouse). Study participants had a blood test and a full medical examination, which consisted of structured questionnaires, information about chronic diseases and a clinical examination. Sera were stored at  $-100^{\circ}\text{C}$  until analyses were performed in a sample of 752 women. This choice of 752 women was based on our budgetarian's capacity to perform the laboratory measure of serum 25OHD concentration. The randomization process was based on the use of a random-number table that generated in an unpredictable, haphazard sequence of number corresponding to the number of subjects included in the study. From this randomized subset of 752 women, all data were available for 744 women.

### 2.2. Muscle strength measures

The procedure consisted of the evaluation of the maximal isometric voluntary contraction (MVC) strength of the dominant side triceps brachii muscle with dynamometers. Before testing, participants were allowed to practice the isometric movements to warm up, and a trained evaluator gave standardized verbal instructions regarding the test procedure. Isometric elbow extension was measured as the force applied at the hand, with the participant seated on a chair and her shoulder and elbow resting on a support flexed at  $90^{\circ}$ . The MVC was recorded in Newton (N) using a statergometer (ADCRO [Association pour le Développement de la Chirurgie Réparatrice et Orthopédique]

electronic statergometer; ADCRO, Valenton, France). Two MVC were recorded seconds apart. Verbal encouragement was given each time to obtain the maximal score. Between-test change of triceps strength was defined as the difference between the first test and the second one as follows "First strength measure – Second strength measure". Triceps brachii muscle fatigability was defined as the loss of more than 5% of the muscle strength between the first test and the second one. This prevented considering a low inter-measure variability of  $\leq 5\%$  as muscle fatigability.

### 2.3. Serum vitamin D assessment

Fasting early morning venous blood was collected from resting participants for the measurement of serum 25OHD concentration, a reliable indicator of vitamin D status [14]. Serum 25OHD concentrations were measured by radioimmunoassay (Incstar Corp., Stillwater, MN). With this method, there is no lipid interference, which is often observed in other non-chromatographic assays of 25OHD. The intra- and interassay precision was 5.2% and 11.3%, respectively (range, 12–50 ng/mL in normal adults aged 20–60 years). Hypovitaminosis D was defined using the three most common definitions in the literature, i.e.  $\leq 10$  ng/mL,  $\leq 20$  ng/mL, and  $\leq 30$  ng/mL [14]. All measurements were performed at the University Hospital of Lyon, France.

### 2.4. Covariates

The following clinical variables were included as potential confounders in the statistical models: age, body mass index (BMI), number of comorbidities, use psychoactive drugs, regular physical activity, and first triceps strength measure. Hyperparathyroidism, serum concentrations of calcium, albumin and creatinine, and the influence of seasons and study centers were also taken into account in the analysis.

#### 2.4.1. Assessment of clinical covariates

Clinical covariates were obtained from a physical examination and a health status questionnaire to target comorbidities (i.e., hypertension, diabetes, dyslipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral vascular disease, cancer, stroke, Parkinson disease and depression). Weight was measured with a beam balance scale, and height with a height gauge. BMI was calculated as weight (kg)/height<sup>2</sup> (m<sup>2</sup>). Participation in a physical activity was considered regular if participants had practiced at least one recreational physical activity (i.e., walking, gymnastics, cycling, swimming or gardening) for at least one hour per week for at least the past month. Women were asked to bring all the medication they were regularly taking to the clinical center [13]. Psychoactive drugs were benzodiazepines, antidepressants or neuroleptics.

#### 2.4.2. Assessment of biological covariates

Serum intact parathyroid hormone (iPTH) was measured by immunochemoluminometric assay (Magic Lite, Ciba Corning Diagnostic, Medfield, MA; normal range for adults 20–60 year of age, 11–55 pg/mL). The intra- and interassay precisions were 5.2–6.8 and 5.0–5.5% respectively. Hyperparathyroidism was defined as iPTH concentrations  $\geq 65$  pg/mL [15].

Serum concentrations of calcium, albumin, and creatinine were determined using automated standard laboratory methods. Because of the high prevalence of hypoalbuminemia in older adults, serum concentrations of albumin and calcium were used to correct the calcium value: corrected calcium = uncorrected calcium +  $[(40 - \text{albumin}) \times 0.02]$ .

### 2.5. Statistical analysis

The participants' characteristics were summarized using means and standard deviations (SD) or frequencies and percentages, as

appropriate. As the number of observations in each group was higher than 40, no transform was applied. Firstly, comparisons between participants separated into two groups based on muscle fatigability (loss of triceps strength between the two tests  $\leq 5\%$  or  $> 5\%$ ) were performed using independent samples *t*-test or Chi-square test, as appropriate. Secondly, a multiple linear regression model was used to examine the cross-sectional association of the serum 25OHD concentration (independent variable) with the between-test change of triceps strength (dependent variable) after adjustment for potential confounders. Thirdly, two multiple (i.e., fully adjusted model, and stepwise backward model) logistic regressions were consecutively used to examine the association between hypovitaminosis D (independent variable) and triceps brachii muscle fatigability (dependent variable) while adjusting for potential confounders. P-values  $< 0.05$  were considered significant. All statistics were performed using SPSS (version 17.0; SPSS, Inc., Chicago, IL).

## 2.6. Ethics

Participants were included after having given their written informed consent for research. The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). The project was approved by the local ethics committee of each center.

## 3. Results

Among 744 women included in the present analysis (mean age  $80.0 \pm 3.5$  years), the prevalence of muscle fatigability was 17.5%. The mean 25OHD concentration was  $17.9 \pm 11.0$  ng/mL. Hypovitaminosis D  $\leq 30$  ng/mL was retrieved among 671 women,  $\leq 20$  ng/mL among 516 women, and  $\leq 10$  ng/mL among 127 women.

As indicated in Table 1, the prevalence of hypovitaminosis D  $\leq 30$  ng/mL was greater among women with muscle fatigability compared to those without (respectively 96.2% versus 88.9%,  $P = .009$ ). In contrast, there was no between-group difference using the other definitions of hypovitaminosis D ( $P = .75$  for hypovitaminosis D  $\leq 20$  ng/mL, and  $P = .45$  for hypovitaminosis D  $\leq 10$  ng/mL). Logically, women

**Table 1**

Characteristics of the randomized sample ( $n = 744$ ) according to triceps fatigability.

	Whole group (n = 744)	Loss of triceps strength between the two tests		P-value*
		≤5% (n = 614)	> 5% (n = 130)	
Clinical measures				
Age (years), mean ± SD	80.0 ± 3.5	80.1 ± 3.5	80.2 ± 3.3	0.78
Body mass index (kg/m <sup>2</sup> ), mean ± SD	25.7 ± 4.4	25.8 ± 4.4	25.4 ± 4.6	0.43
Number of comorbidities <sup>†‡</sup> , mean ± SD	3 ± 2	3 ± 2	3 ± 2	0.90
Use psychoactive drugs <sup>†  </sup> , n (%)	351 (47.2)	295 (48.0)	56 (43.1)	0.30
Regular physical activity <sup>†§</sup> , n (%)	395 (53.1)	331 (53.9)	64 (49.2)	0.33
Triceps strength				
First test <sup>¶</sup> (N/m <sup>2</sup> ), mean ± SD	91.7 ± 30.5	91.7 ± 30.4	91.3 ± 31.2	0.89
Second test <sup>¶</sup> (N/m <sup>2</sup> ), mean ± SD	96.8 ± 32.0	100.7 ± 31.5	78.4 ± 27.8	< 0.001
Serum measures				
25OHD concentration ≤30 ng/mL, n (%)	671 (90.2)	546 (88.9)	125 (96.2)	0.009
25OHD concentration ≤20 ng/mL, n (%)	516 (69.4)	424 (69.1)	92 (70.8)	0.75
25OHD concentration ≤10 ng/mL, n (%)	127 (17.1)	108 (17.6)	19 (14.6)	0.45
Hyperparathyroidism <sup>#</sup> , n (%)	265 (35.6)	220 (35.8)	45 (34.6)	0.79
Calcium concentration <sup>††</sup> (mg/L), mean ± SD	94.2 ± 3.9	94.2 ± 4.0	94.1 ± 3.5	0.76
Albumin concentration (g/L), mean ± SD	45.9 ± 4.7	45.8 ± 4.8	46.3 ± 3.9	0.26
Creatinine concentration (mg/L), mean ± SD	10.1 ± 4.2	10.1 ± 4.5	10.0 ± 2.5	0.79

25OHD: 25-hydroxyvitamin D; SD: standard deviation; \*: comparisons between participants with triceps strength fatigability (i.e., loss of triceps strength  $> 5\%$  between the two tests) and participants without triceps strength fatigability based on Student's *t*-test or Chi-square test, as appropriate; †: obtained from a standardized health status questionnaire; ‡: amongst hypertension, diabetes, dyslipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral vascular disease, cancer, stroke, Parkinson's disease and depression; ||: use benzodiazepines or antidepressants or neuroleptics; §: at least one hour recreational physical activity (walking, gymnastics, cycling, swimming or gardening) per week for the past month or more; ¶: maximal isometric voluntary contraction strength measured with computerized dynamometers expressed in Newton; #: serum intact parathyroid hormone concentration  $\geq 65$  pg/mL; ††: corrected value based on the formula: corrected calcium = uncorrected calcium +  $[(40 - \text{albumin}) \times 0.02]$ ; P-value significant (i.e.  $P < .05$ ) indicated in bold.

**Table 2**

Multiple linear regression showing the cross-sectional association of between-test change of triceps strength (dependent variable) with serum 25-hydroxyvitamin D concentration (independent variable) adjusted for potential confounders\* ( $n = 744$ ).

	Between-test change of triceps strength †		
	$\beta$	95% CI	P-value
Serum 25-hydroxyvitamin D concentration	−0.09	−0.18; −0.01	<b>0.04</b>
Age	−0.15	−0.43; 0.13	0.30
Body mass index	−0.28	−0.50; −0.05	<b>0.02</b>
Number of comorbidities †	−0.06	−0.63; 0.51	0.84
Use psychoactive drugs †§	−0.53	−2.45; 1.39	0.59
Regular physical activity †¶	−1.76	−3.75; 0.23	0.08
First triceps strength measure †#	0.05	0.02; 0.08	<b>0.003</b>
Hyperparathyroidism ††	−0.81	−2.83; 1.21	0.43
Serum calcium concentration †††	0.06	−0.20; 0.31	0.68
Serum albumin concentration	0.13	−0.08; 0.35	0.22
Serum creatinine concentration	−0.18	−0.41; 0.04	0.11

$\beta$ : coefficient of regression corresponding to a change of between-test change of triceps strength†; CI: confidence interval; \*: adjusted for the influence of study center with no significant effect ( $\beta = 0.89$  [95CI: 0.08; 1.71],  $P = .03$ ), and season with no significant effect ( $\beta = -0.21$  [95CI: −1.26; 0.84],  $P = .69$ ); †: defined as 'First strength measure – Second strength measure'; ‡: obtained from a standardized health status questionnaire; ||: amongst hypertension, diabetes, dyslipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral vascular disease, cancer, stroke, Parkinson disease and depression; §: use of benzodiazepines or antidepressants or neuroleptics; ¶: at least one hour recreational physical activity (walking, gymnastics, cycling, swimming or gardening) per week for the past month or more; #: maximal isometric voluntary contraction strength measured with computerized dynamometers at first test; ††: serum intact parathyroid hormone concentration  $\geq 65$  pg/mL; †††: corrected value based on the formula: corrected calcium = uncorrected calcium +  $[(40 - \text{albumin}) \times 0.02]$ ; coefficient of regression  $\beta$  significant (i.e.  $P < .05$ ) indicated in bold.

with muscle fatigability had lower trial 2 mean strength compared to those without muscle fatigability ( $78.4 \pm 27.8$  versus  $100.7 \pm 31.5$ ,  $P < .001$ ).

The multiple linear regression model showed an inverse association between serum 25OHD concentration and between-test change of triceps strength (adjusted  $\beta = -0.09$ ,  $P = .044$ ) (Table 3). The between-

**Table 3**

Univariate and multiple logistic regressions showing the cross-sectional association of triceps brachii muscle fatigability\* (dependent variable) with hypovitaminosis D  $\leq 30$  ng/mL (independent variable), adjusted for potential confounders<sup>‡</sup> (n = 744).

	Triceps brachii muscle fatigability*					
	Fully adjusted model			Stepwise backward model		
	OR	95% CI	P-value	OR	95% CI	P-value
Hypovitaminosis D <sup>†</sup>	3.15	1.24;8.01	<b>0.02</b>	3.11	1.23;7.88	<b>0.02</b>
Age	1.00	0.95;1.06	0.93	–	–	–
Body mass index	0.98	0.93;1.03	0.36	–	–	–
Number of comorbidities <sup>  §</sup>	1.01	0.90;1.12	0.90	–	–	–
Use psychoactive drugs <sup>  ¶</sup>	0.77	0.52;1.15	0.20	–	–	–
Regular physical activity <sup>  #</sup>	0.79	0.52;1.18	0.24	–	–	–
First triceps strength measure <sup>**</sup>	1.00	0.99;1.01	0.94	–	–	–
Hyperparathyroidism <sup>††</sup>	0.91	0.60;1.35	0.65	–	–	–
Serum calcium concentration <sup>**</sup>	0.99	0.94;1.04	0.56	–	–	–
Serum albumin concentration	1.04	0.99;1.08	0.15	–	–	–
Serum creatinine concentration	0.99	0.94;1.05	0.76	–	–	–

OR: odds ratio; CI: confidence interval; \*: defined as loss of triceps strength > 5% between the two tests; †: serum 25-hydroxyvitamin D  $\leq 30$  ng/mL; ‡: adjusted on the influence of study center with no significant effect (OR = 1.09 [95CI: 0.95;1.27], P = .23), and season with no significant effect (OR = 0.94 [95CI: 0.78;1.13], P = .50); ||: obtained from a standardized health status questionnaire; §: amongst hypertension, diabetes, dyslipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral vascular disease, cancer, stroke, Parkinson disease and depression; ¶: use of benzodiazepines or antidepressants or neuroleptics; #: at least one hour recreational physical activity (walking, gymnastics, cycling, swimming or gardening) per week for the past month or more; \*\*: maximal isometric voluntary contraction strength measured with computerized dynamometers at first test; ††: serum intact parathyroid hormone concentration  $\geq 65$  pg/mL; ‡‡: corrected value based on the formula: corrected calcium = uncorrected calcium + [(40–albumin)  $\times$  0.02]; OR significant (i.e. P < .05) indicated in bold.

test change of triceps strength was also associated with the BMI ( $\beta = -0.28$ , P = .02) and the first triceps strength measure ( $\beta = 0.05$ , P = .003) (Table 2).

Lastly, Table 3 reports the results of the multiple logistic regressions between triceps brachii muscle fatigability, hypovitaminosis D  $\leq 30$  ng/mL and covariates, with odds ratio (OR) and confidence intervals (CI). Hypovitaminosis D  $\leq 30$  ng/mL was positively associated with triceps fatigability in the fully adjusted model (fully adjusted OR = 3.15, P = .02), and was the single independent variable retained in the stepwise backward model (adjusted OR = 3.11, P = .02) (Table 3). Additional analyses found no association between triceps fatigability and hypovitaminosis D while using the other definitions (P = .48 for hypovitaminosis D  $\leq 10$  ng/mL; P = .72 for hypovitaminosis D  $\leq 20$  ng/mL).

#### 4. Discussion

The main result of this population-based study in 744 older women was the finding of an inverse association between serum 25OHD concentration and change of triceps strength between two consecutive measurements; hypovitaminosis D  $\leq 30$  ng/mL being independently associated with greater triceps fatigability.

Despite increasing evidence on the effects of vitamin D on muscle health [2] and chronic fatigue syndrome [9,12], only few data are available on the relationship between hypovitaminosis D and skeletal muscle fatigability. To the best of our knowledge, only two studies have examined this issue [16,17]. The first one, an animal study by Kasukawa et al. [16], examined the effects of vitamin D supplementation on calf muscle fatigue in 12 ovariectomized rats. In this study, vitamin D supplementation did not affect muscle fatigue evaluated by electrical stimulation of the sciatic nerve under general anesthesia, and was not associated with changes of the diameter or the composition of muscle fibers [16]. In contrast, the second study, conducted by Askmark et al. among 13 patients with myasthenia gravis [17], reported beneficial effects of vitamin D supplementation (800 IU per day) on myasthenic muscle fatigue, as illustrated by a 38-percent improvement of the Myasthenia Gravis Composite score. Unlike our observational study, both these previous studies were interventional with, in principle, higher level of evidence. However, both these studies were limited by a low number of participants [16,17]. Moreover, although the study in

rodents did effectively measure muscle fatigue [16], the study in middle-aged adults did not assess fatigue *per se*, but rather myasthenic fatigue using a composite score [17]. Thus, the results of the current study provide additional information on the relationship between vitamin D and muscle fatigue in older adults, by reporting an association between hypovitaminosis D and greater loss of triceps strength between two consecutive measurements.

This association was retrieved only with the definition of hypovitaminosis D  $\leq 30$  ng/mL, which is consistent with previous literature. The method for calculating 25OHD reference values, called “health-based reference values”, is to define hypovitaminosis D as the range of serum 25OHD concentrations that are associated with adverse health effects [18]. Due to the multiplicity of the manifestations accompanying hypovitaminosis D, the determination of a single threshold remains yet vain, and various reference values should be considered according to the condition of interest [19]. For instance, a 25OHD concentration of 10 ng/mL is sufficient to prevent rickets and osteomalacia, but a concentration of at least 20 ng/mL is necessary to prevent secondary hyperparathyroidism [20]. Consistently, the threshold at 10 ng/mL is consensual to define vitamin D deficiency (i.e., severe hypovitaminosis D) [14], and the threshold at 20 ng/mL is that used by the World Health Organization (WHO) [21] and the American Institute of Medicine (IOM) [22] to define vitamin D insufficiency. Nevertheless, more recently, Bischoff-Ferrari et al. elegantly showed that a serum 25OHD concentration of at least 30 ng/mL was necessary to prevent the non-bone effects of vitamin D [23]; i.e., the threshold value retained by the US Endocrine Society to define vitamin D insufficiency [24]. Thus, finding an association of muscle fatigability with hypovitaminosis D only with the definition  $\leq 30$  ng/mL confirms the interest of the latter threshold while considering the non-skeletal effects of vitamin D.

Several hypotheses may explain the association between vitamin D and muscle fatigability. A first explanation is that older individuals with greater muscle fatigability are more likely to exhibit limited functional abilities [2] resulting in lower dietary intakes of vitamin D and excessive time spent indoors, with consequent greater risks of hypovitaminosis D [14]. However, our community-dwelling participants were relatively healthy with a high BMI of  $25.7 \pm 4.4$  kg/m<sup>2</sup> and a high score on Lawton's instrumental activities of daily living (IADL) scale of  $6.2 \pm 1.4$  out of 8. Moreover, there were no differences in BMI, IADL score and practice of physical activity according to the 25OHD status.



Alternatively, hypovitaminosis D may influence the muscle ability to pursue effort and maintain constant work. Results of several lines of experimentation support an action of vitamin D on muscles. In particular, the presence of vitamin D receptors (VDRs) has been revealed in muscle cells [5], both in the nucleus and the cytoplasmic membrane [25]. The genomic action of vitamin D appears involved in various phenomena including calcium influx into muscle cells, membrane phosphate transport, phospholipids metabolism, and muscle fiber proliferation and differentiation [26,27]. The nongenomic action of vitamin D is complementary to the genomic one by activating a second messenger in the cyclic AMP and/or diacylglycerol and/or inositol triphosphate and/or arachidonic acid- and by activating protein kinase C. These effects lead to active transportation of calcium into sarcoplasmic reticulum by calcium-ATPase, which enhances the calcium pool necessary for the successive attachments and detachments of myofilaments responsible for muscular contraction [28]. Vitamin D therefore appears to participate in the functional equilibrium of muscle fibers [29]. Further, we recently reported that hypovitaminosis D could aggravate the age-related decrease in muscle regeneration capacity [29] and that vitamin D potentially alters protein anabolism in myotubes [26]. In parallel, other evidence suggests that vitamin D may also improve mitochondrial oxidative function in skeletal muscle [12]. Specifically, it has been reported that vitamin D supplementation augments muscle mitochondrial maximal oxidative phosphorylation after exercise in individuals with hypovitaminosis D [12]. This suggests that changes in mitochondrial oxidative phosphorylation in skeletal muscle could be partly responsible for the muscle fatigue and the inability to maintain constant effort experienced by participants with hypovitaminosis D in our study.

We found a low mean 25OHD concentration of  $17.9 \pm 11.0$  ng/mL in this cohort of community-dwelling older women. Older adults are at high risk of hypovitaminosis D [1], and the prevalence of hypovitaminosis D is frequently underestimated [14]. As a consequence, the prevalence of hypovitaminosis D might be higher in older community-dwellers than previously reported. For this reason and because of the adverse outcomes accompanying hypovitaminosis D (potentially including muscle fatigability), our results emphasize the need for implementation of standard strategies to prevent and treat hypovitaminosis D in geriatric patients, even in autonomous older adults living at home.

It has been repeatedly reported that lower serum 25OHD concentrations result in greater fall risk among older adults [2]. This association has been explained thus far by hypovitaminosis D-related lower muscle strength [5] and motor control disorders [2], with adverse consequences on static and dynamic posture. Based on our present findings, we propose that falls in the case of hypovitaminosis D could also result from the inability of striated muscles to pursue effort and to maintain constant work when exercise is prolonged. This novel orientation of research may offer a powerful mechanism to better understand the pathophysiology of falls in older adults with hypovitaminosis D, and to act on their healthcare needs to maintain function late in life.

Our results confirmed that a low BMI is associated with greater between-test change of triceps strength. Undernourishment is a recognized cause of fatigability while aging [30]. This consensual result strengthens the consistency of our study and confirms the relevance of the association found between hypovitaminosis D and muscle fatigability. Regardless, some potential limitations of our study should be considered. The study cohort was restricted to relatively vigorous older women who may be unrepresentative of older adults in general. Moreover, the study participants may have been more motivated, with a greater interest in personal health issues, than the general population of older adults. The use of a cross-sectional design prevents any causal inference from the present study. We used only a single measurement of muscle fatigability, which may result in non-differential measurement error and an underestimation of the strength of the true associations.

Finally, although we were able to control for important characteristics that could modify the association between vitamin D and muscle fatigability, residual potential confounders might still be present.

In conclusion, lower serum 25OHD concentrations were associated with muscle fatigability in community-dwelling older women. Further prospective studies with different senior cohorts are warranted to assess a direct effect of hypovitaminosis D on the muscular ability to pursue effort and to maintain constant work, and its impact in terms of fall risk in older individuals.

## Contributors

G. Duval undertook analysis and interpretation of data, and drafted the manuscript.

Y. Rolland undertook critical revision of the manuscript for important intellectual content.

A.M. Schott was responsible for obtaining funding and acquisition of data, provided administrative and technical support, and undertook critical revision of the manuscript for important intellectual content.

H. Blain undertook critical revision of the manuscript for important intellectual content.

P. Dargent-Molina undertook critical revision of the manuscript for important intellectual content.

S. Walrand undertook critical revision of the manuscript for important intellectual content.

G. Duque undertook critical revision of the manuscript for important intellectual content.

C. Annweiler was responsible for the study concept and design, and its supervision, undertook statistical analysis, analysis and interpretation of data, and drafted the manuscript.

## Conflict of interest

All authors declare that they have no conflict of interest.

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## Ethical approval

Participants were included after having given their written informed consent for research. The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). The project was approved by the local ethics committee of each center.

## Provenance and peer review

Peer review was directed by Leon Flicker independently of Cedric Annweiler, an author and *Maturitas* editor, who was blinded to the process.

## Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

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Grandjean and Ribot (Toulouse).

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