

# The association of frailty with serum 25-hydroxyvitamin D and parathyroid hormone levels in older European men

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## Abstract

**Background:** the link between the vitamin D endocrine axis and frailty remains undefined, with few studies examining the joint effect of vitamin D and parathyroid hormone (PTH) levels. Our objective was to determine the association of frailty with serum 25-hydroxyvitamin D (25(OH)D) and PTH.

**Setting:** cross-sectional analysis within the European Male Ageing Study (EMAS).

**Participants:** a total of 1,504 community-dwelling men aged 60–79 years.

**Methods:** frailty was classified using a frailty phenotype (FP) and frailty index (FI). The association of frailty with 25(OH)D and PTH was examined using multinomial logistic regression; individual FP criteria with 25(OH)D and PTH using binary logistic regression. Results were expressed as relative odds ratios (ROR) and 95% confidence intervals (CIs) for multinomial; odds ratios (OR) and 95% CIs for binary models.

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**Results:** using the FP, 5.0% of subjects were classified as *frail* and 36.6% as *prefrail*. Lower levels of 25(OH)D were associated with being *prefrail* (per 1 SD decrease: ROR = 1.45; 95% CI: 1.26–1.67) and *frail* (ROR = 1.89; 95% CI: 1.30–2.76), after adjusting for age, centre and health and lifestyle confounders (*robust* group = base category). Higher levels of PTH were associated with being frail after adjustment for confounders (per 1 SD increase: ROR = 1.24; 95% CI: 1.01–1.52). Comparable results were found using the FI. Among the five FP criteria only sarcopenia was not associated with 25(OH)D levels, while only weakness was associated with PTH.

**Conclusion:** lower 25(OH)D and higher PTH levels were positively associated with frailty in older men. Prospective data would enable the temporal nature of this relationship to be explored further.

**Keywords:** frailty, vitamin D, parathyroid hormone, population-based, male health, ageing, EMAS, older people

## Introduction

Frailty is conceptualised as a multidimensional syndrome of the loss of physical ability and health resulting in increased vulnerability [1]. Some 20–30% of older people ( $\geq 75$  years) are considered frail and this proportion increases with age [2]. Vitamin D inadequacy has also been reported to be widespread among older people, with a reported prevalence of 30–90% depending on the threshold used [3]. Recent investigations have suggested a possible aetiological role for vitamin D in the development of frailty [4, 5].

A report from the Invecchiare in Chianti (InCHIANTI) study found a relationship between lower levels of vitamin D and higher risk of frailty in older Italian men [6], while Wilhelm-Leen *et al.* observed a similar result in a large sample of non-institutionalised older North American adults [4]. A recent study in older US women found a cross-sectional relationship between low levels of vitamin D and frailty [7], and associations between low vitamin D levels and frailty have also been found among older Taiwanese adults [8] recruited into a trial of integrative geriatric care. The majority of these reports measured serum levels of 25-hydroxyvitamin D (25(OH)D), as it is considered the best indicator of the vitamin D status [3].

Any aetiological link between vitamin D, parathyroid hormone (PTH) and frailty remains undefined and few studies have examined the joint effect of vitamin D and PTH levels on physical performance and frailty [9, 10]. We used baseline data from the population-based European Male Ageing Study (EMAS) to determine the association of serum 25(OH)D and PTH levels with the frailty status, and examine which component criteria of our phenotypic definition of frailty were associated with the vitamin D endocrine axis.

## Methods

### Participants

The response rates and assessments in EMAS have been described previously [11]. Briefly, 3,369 men aged 40–79 years were recruited from population-registers in eight centres: Florence (Italy), Leuven (Belgium), Łódź (Poland), Malmö (Sweden), Manchester (UK), Santiago de Compostela (Spain), Szeged (Hungary) and Tartu (Estonia). Stratified

random sampling was used to attain equal numbers in each of the four age decades. Subjects were invited to take part by letter, which included a short-postal questionnaire. Participants completed an interviewer-assisted questionnaire, various clinic-based performance measures and provided a fasting blood sample. Ethical approval was obtained in accordance with institutional requirements in each centre. Because frailty is uncommon in younger men, analyses were restricted to those aged  $\geq 60$  years.

### Assessments

The postal questionnaire captured demographic, health and lifestyle information, including age leaving full-time education, tobacco use and alcohol consumption. Subjects were also asked whether they were currently being treated for cardiovascular diseases, hypertension, bronchitis, asthma, peptic ulcer, epilepsy, diabetes, cancer, liver, kidney or prostate diseases and thyroid disorders.

The interviewer-assisted questionnaire included the 36-item Short Form survey (SF-36) [12], Physical Activity Scale for the Elderly (PASE) [13] and Beck's Depression Inventory-II (BDI) [14]. Functional assessments included Reuben's Physical Performance test (PPT) [15] and Tinetti's balance and postural stability index [16]. Anthropometric measurements included height, weight, mid-upper arm circumference and triceps skin fold thickness.

### Frailty

Frailty status was determined using Fried's phenotypic definition [17] based on five criteria: exhaustion, weakness, slowness, low activity and sarcopenia. Details of the EMAS frailty phenotype (FP) criteria are reported elsewhere [18]. 'Exhaustion' was defined from the BDI 'energy' and 'fatigue' items, 'weakness' from the Tinetti 5 chair stand test (threshold = slowest 10% from 65+ years, or unable to complete the test), 'slowness' from the PPT 50 foot walk (threshold = slowest 20% stratified by height for 65+ years), 'low activity' from the PASE score (threshold = lowest 20% for 65+ years) and 'sarcopenia' from mid-upper arm muscle circumference (mid-upper arm circumference  $- 3.14 \times$  triceps skinfold thickness; threshold = lowest 10% for 65+ years). The EMAS-FP was categorised as: 0 criteria = *robust*, 1–2

criteria = *prefrail* and 3 + criteria = *frail*. We have previously shown that the EMAS-FP is associated with age, falls and impaired quality-of-life [18].

We also assessed frailty using the concept of deficit accumulation by calculating a frailty index (FI). The EMAS-FI has been described previously [19], and represents the number of health deficits present divided by the number of health deficits considered. Forty-three deficits were included, characterising adverse symptoms, signs or functional impairments. The EMAS-FI included elements from the SF-36, BDI, PPT and Tinetti scales in addition to self-reported morbidities, medication use and cognition [19]. Binary variables were coded as 0 indicating the absence and 1 the presence of a deficit. For variables that included an intermediate response (e.g. *sometimes* or *maybe*), an additional value of 0.5 was used. Continuous variables were dichotomised based on the distribution of scores; cut-points were the worst-performing 10th centile [19]. To compare associations between vitamin D and the two frailty definitions, the FI was categorised as: *robust*,  $\geq 0$  FI  $\leq 0.2$ ; *prefrail*,  $>0.2$  FI  $\leq 0.35$  and *frail*,  $>0.35$  FI, using thresholds suggested by Kulminski *et al.* [20].

### Assessment of 25-hydroxyvitamin D and PTH

A fasting blood sample was obtained from all subjects. Processed serum was stored at  $-80^{\circ}\text{C}$  and shipped frozen to central laboratories for the measurement of 25(OH)D (Katholieke Universiteit Leuven, Belgium) and PTH (University of Santiago de Compostela, Spain). Serum 25(OH)D levels were determined by radioimmunoassay (DiaSorin, Stillwater, MN, USA), with intra- and inter-assay coefficients of variation (CV) of 11 and 8%, respectively, and a detection limit of 5.0 nmol/l. Serum PTH was assayed using a chemiluminescence immunoassay (Bio-Intact PTH, Quest Diagnostics, Madison, NJ, USA), with intra- and inter-assay CVs of 6 and 2.8%, respectively, and a detection limit of 1.5 pg/ml.

### Statistical methods

Statistical analyses were conducted using STATA SE v10.1 (StataCorp, College Station, TX, USA). Subjects aged  $<60$  years ( $n = 1,700$ ) and those with missing EMAS-FP data ( $n = 165$ ) were excluded, leaving 1,504 men in this analysis. Smoking was categorised as 'current versus never/ex-smoker', alcohol consumption as ' $\geq 5$  days/week versus  $<5$  days/week', season as 'spring, summer, autumn and winter', and morbidities as 'none versus one or more'. ANOVA or Kruskal–Wallis was used to test associations between frailty status and continuous variables and the Chi-square test for associations with categorical variables.

Multinomial logistic regressions were used to explore the association of 25(OH)D and PTH levels with FP or FI frailty status (dependent variable). We adjusted initially for age and centre and then for additional variables significantly associated with the frailty status, including smoking status and comorbidities. 25(OH)D and PTH were converted to

z-scores providing a 'relative' measure of the magnitude of each association with the frailty outcome (per SD change), independent of units of concentration.

Data were also analysed after categorising 25(OH)D levels as: sufficient, 25(OH)D  $\geq 75$  nmol/l; suboptimal, 25(OH)D 50.0–74.9 nmol/l and insufficient, 25(OH)D  $<50$  nmol/l. Although no current consensus on optimal serum 25(OH)D levels exist, vitamin D insufficiency is considered by most experts as a 25(OH)D concentration of  $<50$  nmol/l [21]. Results were expressed as relative odds ratios (ROR) and 95% confidence intervals (CIs) for multinomial models. We also examined the individual components of the EMAS-FP to determine associations with 25(OH)D and PTH using binary logistic regression following the same strategy used in the multinomial models, with results presented as odds ratios (OR) and 95% CIs.

## Results

### Subject characteristics

Details of the 1,504 men included in the analysis are shown in Table 1. Based on the EMAS-FP definition, 58.2% of men were *robust*, 36.7% *prefrail* and 5.1% *frail*. The median (inter-quartile range) for the FI was 0.15 (0.15).

### Vitamin D, PTH and frailty

There were significant differences in 25(OH)D and PTH levels across FP categories ( $P < 0.001$ ), see Table 1. The prevalence of insufficient 25(OH)D ( $<50$  nmol/l) was 33.2% in the *robust*, 45.9% in the *prefrail* and 62.3% in the *frail* group. Frailty status was also associated with age (highest among *frail* subjects) and height (lowest among *frail* subjects). *Prefrail* and *frail* subjects were more likely to be current smokers and have one or more morbidities.

Using the EMAS-FP as the dependent variable and adjusting for age and centre (*robust* = base category) lower levels of 25(OH)D (per 1 SD decrease) were associated with being *prefrail* (ROR = 1.47; 95% CI: 1.29–1.68) and *frail* (ROR = 1.85; 95% CI: 1.31–2.60), see Table 2. These associations persisted after additional adjustment for smoking, morbidities and PTH. The ROR indicates the likelihood of being in one outcome category (*prefrail* or *frail*) with reference to the *robust* category (base category). Therefore, for each 1 SD decrease in 25(OH)D, the odds of being *prefrail* over being *robust* increases by 1.47, and by 1.85 for being *frail* over *robust*. Higher levels of PTH (per 1 SD increase) were associated with being *prefrail* (ROR = 1.13; 95% CI: 1.01–1.27) and *frail* (ROR = 1.37; 95% CI: 1.13–1.66) (Table 2). After additional adjustment for smoking, morbidities and 25(OH)D, PTH remained significantly associated with *frailty* (ROR = 1.24; 95% CI: 1.01–1.52) but not *prefrailty* (ROR = 1.05; 95% CI: 0.93–1.18).

Both suboptimal (25(OH)D  $\geq 50$  and  $<75$  nmol/l) and insufficient (25(OH)D  $<50$  nmol/l) vitamin D levels were associated with *prefrailty* and *frailty*. After adjustment for age

Table 1. Subject characteristics: by frailty status (frailty phenotype criteria)

	Total sample (n = 1504)	Robust 876 (58.2%)	Prefrail 552 (36.7%)	Frail 76 (5.1%)	P-value
Mean (SD) <sup>a</sup>					
Age (years)	69.5 (5.7)	68.4 (5.5)	70.9 (5.6)	72.9 (4.7)	<0.001
Age left education (years)	20.8 (8.8)	21.0 (8.9)	20.5 (8.9)	19.7 (8.0)	0.156
Height (m)	171.3 (7.0)	171.8 (6.9)	170.8 (6.9)	169.5 (7.9)	0.002
Weight (kg)	81.7 (13.1)	82.1 (11.6)	81.4 (14.9)	79.0 (16.5)	0.123
Body mass index (kg/m <sup>2</sup> )	27.8 (4.0)	27.8 (3.4)	27.9 (4.6)	27.3 (4.8)	0.548
25(OH)D (nmol/l)	62.9 (31.4)	68.1 (32.4)	56.3 (27.7)	49.6 (32.6)	<0.001
PTH (pg/ml)	30.6 (15.2)	29.4 (13.1)	31.9 (16.5)	36.3 (24.7)	<0.001
Frailty index	0.18 (0.12)	0.13 (0.09)	0.22 (0.12)	0.37 (0.11)	<0.001
Number (%) <sup>b</sup>					
Co-morbidities (1 or more)	1058 (71.3)	565 (65.2)	426 (78.5)	67 (88.2)	<0.001
Smoking status (current)	209 (14.0)	99 (11.4)	91 (16.8)	19 (25.0)	<0.001
Alcohol intake (≥5 days/week)	366 (24.6)	229 (26.2)	122 (22.5)	15 (20.3)	0.193
Season					
Winter	440 (29.3)	249 (28.4)	173 (31.5)	18 (24.0)	0.079
Spring	273 (18.2)	174 (19.8)	84 (15.3)	15 (20.0)	
Summer	269 (17.9)	170 (19.4)	86 (15.7)	13 (17.3)	
Autumn	520 (34.6)	285 (32.5)	206 (37.5)	29 (38.7)	
25(OH)D levels					
Sufficient: 25(OH)D ≥75 nmol/l	406 (28.1)	295 (34.9)	104 (19.6)	7 (10.1)	<0.001
Suboptimal: 25(OH)D ≥50 and <75 nmol/l	472 (32.7)	270 (31.9)	183 (34.5)	19 (27.5)	
Insufficient: 25(OH)D <50 nmol/l	567 (39.2)	281 (33.2)	243 (45.9)	43 (62.3)	

25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; SD, standard deviation.

Morbidities included heart conditions, high blood pressure, stroke, cancer, bronchitis, asthma, peptic ulcer, epilepsy, diabetes, and liver, kidney and prostate diseases.

<sup>a</sup>P-value for continuous variables from ANOVA or Kruskal–Wallis.

<sup>b</sup>P-value for categorical variables from Chi-square test of independence.

Table 2. Multinomial logistic regression: association of frailty status (frailty phenotype) with 25(OH)D and PTH

	Model I		Model II	
	Prefrail versus Robust ROR (95% CI)	Frail versus Robust	Prefrail versus Robust ROR (95% CI)	Frail versus Robust
25(OH)D (per 1 SD decrease)	1.47 (1.29–1.68)***	1.85 (1.31–2.60)***	1.45 (1.26–1.67)***	1.89 (1.30–2.76)**
PTH (per 1 SD increase)	1.13 (1.01–1.27)*	1.37 (1.13–1.66)**	1.05 (0.93–1.18)	1.24 (1.01–1.52)*
25(OH)D (nmol/l): categories				
Sufficient (≥75)	Reference	Reference	Reference	Reference
Suboptimal (≥50 and <75)	1.89 (1.39–2.56)***	2.63 (1.07–6.51)*	1.90 (1.38–2.60)***	3.55 (1.27–9.90)*
Insufficient (<50)	2.37 (1.74–3.23)***	5.34 (2.25–12.7)***	2.22 (1.61–3.06)***	5.74 (2.12–15.6)**

SD, standard deviation; CI, confidence interval.

Multinomial logistic regression models: Model I adjusted for age and centre. Model II adjusted for age, centre, smoking status, co-morbid conditions; 25(OH)D models additionally adjusted for PTH, PTH model additionally adjusted for 25(OH)D.

For 25(OH)D and PTH as continuous variables, 'RORs' correspond to a 1 SD decrease in 25(OH)D or PTH. Additional adjustment for BMI or season did not markedly change the magnitude or significance of the associations (data not shown).

\*P < 0.05.

\*\*P < 0.01.

\*\*\*P < 0.001.

and centre the ROR of being *prefrail* over *robust* for those with suboptimal compared with sufficient (25(OH)D ≥75 nmol/l: reference category) vitamin D levels was 1.89 and for insufficient compared with sufficient levels the ROR was 2.37. These RORs were higher for the comparison between *frail* and *robust*. Further adjustment for smoking, morbidities and PTH did not markedly change the magnitude of these associations (Table 2).

The associations between frailty status, using the EMAS-FI, and 25(OH)D and PTH are summarised in

Table 3. The results broadly agreed with those seen using the EMAS-FP, although the magnitude of some associations, particularly between 25(OH)D categories and FI frailty status (Table 3), appeared more modest than those seen using the FP (Table 2).

### Vitamin D, PTH and components of EMAS-FP

The associations of individual FP criteria with both 25 (OH)D and PTH are shown in Table 4. After adjustment



**Table 3.** Multinomial logistic regression: association of frailty status (frailty index) with 25(OH)D and PTH

	Model I		Model II	
	<i>Prefrail</i> versus <i>Robust</i> ROR (95% CI)	<i>Frail</i> versus <i>Robust</i>	<i>Prefrail</i> versus <i>Robust</i> ROR (95% CI)	<i>Frail</i> versus <i>Robust</i>
25(OH)D (per 1 SD decrease)	1.26 (1.09–1.46)**	1.48 (1.14–1.93)**	1.23 (1.05–1.43)*	1.47 (1.10–1.95)**
PTH (per 1 SD increase)	1.13 (0.99–1.28)	1.37 (1.17–1.61)***	1.06 (0.93–1.21)	1.28 (1.08–1.52)**
25(OH)D (nmol/l): categories				
Sufficient ( $\geq 75$ )	Reference	Reference	Reference	Reference
Suboptimal ( $\geq 50$ and $< 75$ )	1.31 (0.92–1.86)	1.14 (0.62–2.12)	1.29 (0.89–1.88)	1.15 (0.60–2.23)
Insufficient ( $< 50$ )	1.87 (1.33–2.65)***	2.35 (1.32–4.20)**	1.69 (1.16–2.45)**	2.11 (1.12–3.97)*

SD, standard deviation; CI, confidence interval.

Multinomial logistic regression models: Model I adjusted for age and centre. Model II adjusted for age, centre, smoking status, co-morbid conditions; 25(OH)D models additionally adjusted for PTH, PTH model additionally adjusted for 25(OH)D.

For 25(OH)D and PTH as continuous variables, 'RORs' correspond to a 1 SD decrease in 25(OH)D or PTH.

*Robust*:  $\geq 0.2$ , *Prefrail*:  $< 0.2$  FI  $\leq 0.35$ , *Frail*: FI  $> 0.35$ . Additional adjustment for BMI or season did not markedly change the magnitude or significance of the associations (data not shown).

\* $P < 0.05$ .

\*\* $P < 0.01$ .

\*\*\* $P < 0.001$ .

for age and centre lower levels of 25(OH)D (continuous or categorical variable) were associated with weakness, low walking speed, exhaustion and low activity. Additional adjustment for smoking, morbidities and PTH did not markedly change these relationships. Subjects with insufficient vitamin D levels ( $< 50$  nmol/l) versus those with sufficient vitamin D ( $\geq 75$  nmol/l) were more likely to be weak (ROR = 1.84; 95% CI: 1.02–3.32), have a low walking speed (ROR = 3.03; 95% CI: 2.04–5.25), exhaustion (ROR = 2.92; 95% CI: 1.65–5.18) and low activity (ROR = 2.15; 95% CI: 1.41–3.28). Higher PTH levels were associated only with weakness in both age and centre adjusted models (ROR = 1.34; 95% CI: 1.16–1.54), and following adjustment for smoking, morbidities and 25(OH)D (ROR = 1.28; 95% CI: 1.11–1.49).

## Discussion

In this population-based study of older European men, we observed a significant association of lower levels of 25(OH)D and higher levels of PTH with frailty using two different frailty definitions. We also observed significant associations between low 25(OH)D levels and most of the individual FP criteria.

Our data are consistent with previous studies showing associations between 25(OH)D and frailty. Both low levels of dietary and serum vitamin D have been associated with prevalent and incident frailty in mixed European cohorts and in disabled elderly women, using the Fried FP and a related model [6, 22, 23]. Other non-European studies [4, 5, 8] have shown positive associations between low vitamin D and frailty. Our data extend these to a diverse cohort of older men from different regions and cultures, and transitional versus non-transitional European countries.

Our data suggest a positive association between the component criteria of the EMAS-FP and low vitamin D,

except sarcopenia. Other studies have shown inconsistent results between individual frailty components and low vitamin D levels. Shardell *et al.* [6] observed that low vitamin D levels were associated with two individual components of frailty; low activity and slowness, while Ensrud *et al.* [5] found low levels of 25(OH)D were associated with weakness in addition to the components identified by Shardell *et al.* However, the assessment of the frailty criteria differed between these studies. A recent study [24] involving a population-based sample of men failed to find significant independent associations between serum 25(OH)D concentrations and physical function (walking speed and chair stand).

The observed cross-sectional associations between 25(OH)D levels and frailty can be interpreted in a number of ways. Low serum 25(OH)D concentrations may be a 'risk marker' of health status, mechanistically separate from the development of frailty. Indeed, low levels of 25(OH)D have been associated with various unfavourable health outcomes, including hypertension [25], increased cancer risk [26] and diabetes [27]. Conversely, frailty itself may contribute to lower 25(OH)D by reducing levels of outdoor activity and sunlight exposure.

The association between frailty and low 25(OH)D could possibly be linked to active vitamin D metabolites down-regulating inflammatory markers such as interleukin-2 and interleukin-12 [6, 28]. Hence, the effects of low 25(OH)D on muscle may be mediated by pro-inflammatory cytokines which are known to impact on physical performance and muscle strength [29]. Low vitamin D levels may also influence frailty indirectly through secondary hyperparathyroidism. Patients with primary hyperparathyroidism display decrements in muscle function that can be improved by parathyroidectomy [30] and elevated PTH levels have been linked to frailty and reduced physical function [6, 9, 10]. In our study, after adjusting for age and other confounders, we found a positive association between PTH and frailty. The magnitude of this relationship appeared to be more modest than that seen with 25(OH)D and was limited to a

**Table 4.** Logistic regression: associations between components of frailty phenotype and 25(OH)D and PTH

	Model I OR (95% CI)	Model II
.....		
Weakness		
25(OH)D (per 1 SD decrease)	1.38 (1.09–1.73)**	1.18 (0.94–1.49)
PTH (per 1 SD increase)	1.34 (1.16–1.54)***	1.28 (1.11–1.49)**
25(OH)D (nmol/l): categories		
Sufficient ( $\geq 75$ )	Reference	Reference
Suboptimal ( $\geq 50$ and $< 75$ )	2.52 (1.44–4.41)**	2.24 (1.27–3.96)**
Insufficient ( $< 50$ )	2.52 (1.42–4.46)**	1.84 (1.02–3.32)*
Low walking speed		
25(OH)D (per 1 SD decrease)	1.68 (1.38–2.05)***	1.71 (1.39–2.11)***
PTH (per 1 SD increase)	1.11 (0.97–1.28)	1.02 (0.87–1.18)
25(OH)D (nmol/l): categories		
Sufficient ( $\geq 75$ )	Reference	Reference
Suboptimal ( $\geq 50$ and $< 75$ )	2.00 (1.26–3.17)**	2.07 (1.28–3.34)**
Insufficient ( $< 50$ )	3.44 (2.20–5.40)***	3.03 (2.04–5.25)***
Sarcopenia		
25(OH)D (per 1 SD decrease)	1.23 (0.98–1.54)	1.17 (0.92–1.49)
PTH (per 1 SD increase)	1.13 (0.97–1.32)	1.12 (0.95–1.32)
25(OH)D (nmol/l): categories		
Sufficient ( $\geq 75$ )	Reference	Reference
Suboptimal ( $\geq 50$ and $< 75$ )	1.13 (0.66–1.94)	1.10 (0.62–1.93)
Insufficient ( $< 50$ )	1.38 (0.82–2.33)	1.31 (0.70–2.11)
Exhaustion		
25(OH)D (per 1 SD decrease)	1.52 (1.21–1.91)***	1.59 (1.24–2.03)***
PTH (per 1 SD increase)	1.12 (0.96–1.30)	1.02 (0.86–1.20)
25(OH)D (nmol/l): categories		
Sufficient ( $\geq 75$ )	Reference	Reference
Suboptimal ( $\geq 50$ and $< 75$ )	1.75 (1.00–3.05)*	1.96 (1.09–3.54)*
Insufficient ( $< 50$ )	2.78 (1.64–4.74)***	2.92 (1.65–5.18)**
Low activity		
25(OH)D (per 1 SD decrease)	1.34 (1.13–1.59)**	1.38 (1.15–1.65)**
PTH (per 1 SD increase)	1.06 (0.93–1.21)	1.02 (0.89–1.16)
25(OH)D (nmol/l): categories		
Sufficient ( $\geq 75$ )	Reference	Reference
Suboptimal ( $\geq 50$ and $< 75$ )	1.58 (1.05–2.38)*	1.70 (1.11–2.60)*
Insufficient ( $< 50$ )	2.12 (1.43–3.17)***	2.15 (1.41–3.28)***

SD, standard deviation; CI, confidence interval.

Binary logistic regression models: Model I adjusted for age and centre. Model II adjusted for age, centre, smoking, co-morbid conditions; 25(OH)D models additionally adjusted for PTH, PTH models additionally adjusted for 25(OH)D.

For 25(OH)D and PTH as continuous variables, 'ORs' correspond to a 1 SD decrease in 25(OH)D or PTH. Additional adjustment for BMI or season did not markedly change the magnitude or significance of any associations (data not shown).

\* $P < 0.05$ .

\*\* $P < 0.01$ .

\*\*\* $P < 0.001$ .

significant difference only between the *frail* and *robust* groups. With respect to the component criteria of the FP, PTH levels were only significantly associated with 'weakness'. Whether any effect on muscle function is mediated by hypovitaminosis D secondary to hyperparathyroidism, or by a direct effect of PTH, e.g. increased intracellular calcium concentrations, remains unknown.

Our data suggest that *frail* individuals have lower vitamin D levels than those in *robust* health. Other cross-sectional studies have shown that reduced levels of serum 25(OH)D are associated with lower muscle strength and disability in older men and women [31, 32], and vitamin D insufficiency has been linked prospectively with an increased risk of falling [33]. Insufficient serum vitamin D may, therefore, contribute to some of the adverse outcomes

linked with frailty, although interventional studies are required to confirm or refute this.

Our study had a number of strengths. Subjects were recruited from population sampling frames and standardised methods used across centres both in the design and conduct, the questionnaire instruments and clinical assessments. However, several limitations should be considered when interpreting the results. Our frailty criteria differed from the original model, although unlike self-reported weight loss, our assessment of sarcopenia relied on objective measurement. The response rate in EMAS was 41%, and participants may have differed with respect to biomarkers and prevalence of frailty components compared with non-participants. However, any such selection bias should not influence the associations seen, which were based on an internal

comparison of responders. Our study was cross-sectional precluding any determination of the temporal nature of the associations, for which prospective data are required. Finally, the results were obtained from a predominantly Caucasian population and should be extrapolated cautiously.

In summary, lower levels of serum 25(OH)D and higher levels of PTH were associated with frailty in older European men, largely independent of health confounders. Further studies are needed to examine the clinical significance of the relationship between the vitamin D endocrine axis and frailty.

## Key points

- Lower levels of 25(OH)D and higher levels of PTH were associated with an increased prevalence of frailty among older men.
- The association with the vitamin D endocrine axis was similar whether frailty was defined as a phenotype or index.
- The individual criteria constituting the FP were more strongly associated with 25(OH)D as compared with PTH.
- The aetiology of the relationship between vitamin D and frailty requires further study.

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## Conflicts of interest

None declared.

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## Central and peripheral fat and subclinical vascular damage in older women

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### Abstract

**Objective:** the aim of this study was to evaluate the relationship between fat distribution and arterial compliance in a group of elderly women, in particular to test a possible independent role of abdominal fat mass and peripheral fat mass on sub-clinical vascular damage, defined by a pulse wave velocity (PWV) >12 m/s.

**Methods:** in 96 women with age range 60–80 years ( $68.65 \pm 4.98$  years) and BMI range from 18.8 to  $41.2 \text{ kg/m}^2$  ( $27.07 \pm 4.61 \text{ kg/m}^2$ ), we evaluated the body mass index, waist circumference, systolic and diastolic blood pressure, fasting glucose, cholesterol, LDL and HDL cholesterol, triglycerides and body composition by dual energy X-ray absorptiometry (DXA). Arterial stiffness was assessed by carotid-femoral (PWVcf) and carotid-radial pulse wave velocity (PWVcr).

**Results:** significant associations were found between PWVcf, age, waist circumference, BMI and trunk fat assessed by DXA, as well as TG and HDL cholesterol. After adjustment for the total fat mass a negative statistically significant association between PWVcf and leg fat mass was shown. In multiple regression analyses the mean arterial pressure, trunk fat