

## Incidence and Risk Factors for Frailty in the Community-Dwelling Elderly Population. A Two-Year Follow-Up Cohort Study

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### Abstract

**Background:** Frailty is a highly prevalent geriatric syndrome and a major public health problem. Designing effective preventive measures requires an understanding of frailty mechanisms and risk factors.

**Objective:** To estimate the incidence of frailty and identify the main risk factors for frailty in community-dwelling elderly individuals.

**Design:** Cohort study followed up over 2 years.

**Participants:** Non-frail community-dwelling individuals aged 75 years and older.

**Measurements:** Socio-demographic variables, co-morbidities, lifestyle, nutritional status, anabolic hormones, inflammatory markers, physical exercise and body composition. Frailty, assessed annually, was defined according to Fried criteria.

**Results:** 278 subjects were recruited (mean age 79.9 years; 42.8% women). Frailty incidence was estimated as 6.8 new cases/100 person-years. Risk factors for frailty were being female, arthrosis, depression, dyspepsia, number of medications, being unable to stand on 1 foot for 5 seconds, a positive Timed Up-and-Go test, a Barthel Index score <90, a high waist-hip ratio, high cholesterol and interleukin-6 levels and low glomerular filtration. Physical exercise was a protective factor for frailty. Risk factors for frailty in men were number of comorbidities, tricipital skinfold and previous handgrip, and in women, insulin resistance and cortisol levels.

**Conclusion:** The fact that certain modifiable risk factors for frailty were identified would suggest that better control of underlying diseases and inflammatory processes, a review of prescribed medications, physical exercise and correction of obesity and hypercholesterolaemia could be effective interventions to reduce frailty in community-dwelling elderly subjects. However, the effectiveness of such interventions needs to be demonstrated by well-designed clinical trials.

**Keywords:** Frailty; Incidence; Risk factors; Elderly; Functional capacity

### Introduction

Frailty is a geriatric syndrome characterized by increased vulnerability to stressors [1]. Its prevalence, which has been estimated at 11% for community-dwelling people aged 65 years and older [2], increases with age and is higher for women than for men. Frail people are at greater risk of falls, functional decline, disability, dependence, institutionalization and death [3,4] and are heavy consumers of healthcare and social resources [5]. Because of population ageing, frailty and its consequences have become a public health problem that needs to be addressed by healthcare systems [6]. The causes of frailty, however, are not well understood. Co-morbidities, certain inflammatory processes, changes in body composition, hormonal imbalances, loss of appetite and metabolic disorders have been suggested as possible risk factors for frailty [7]. Some authors [8] consider frailty to derive from an accumulation of unrelated diseases, dysfunctions and disabilities, while others [9] consider frailty to be a unique pathophysiological process involving the breakdown of homeostatic mechanisms, with muscle wasting as the major component of the frailty phenotype. Loss of muscle mass and strength has been associated with low physical activity, malnutrition, chronic inflammatory processes and falling anabolic hormone levels [10,11]. However, the contribution and relevance of each of these components in the genesis of sarcopenia and frailty is not well established. In fact, the natural history of frailty is little

known, as well as its incidence. On the other hand, sex differences exist not only in the prevalence of frailty but also in body composition and muscle mass, hormonal decline and other co-morbidities, suggesting that the pathophysiological mechanisms of frailty may differ between men and women [2,12].

To help bridge the gap in terms of this absent information, we planned a study with the following objectives: a) to estimate the incidence of frailty in community-dwelling individuals  $\geq 75$  years of age; b) to describe transition from one frailty status to another in this population over a two-year period; c) to identify the main risk factors for frailty in community-dwelling elderly individuals; and d) to assess differences in risk factors according to sex.

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## Materials and Methods

### Study design and population

An observational and prospective study was performed in which a cohort of community-dwelling non-frail subjects aged 75 years and older was followed up for 2 years. Potential participants were randomly pre-selected from the databases of 3 primary care centres in the municipalities of Mataró and Argentona (Barcelona, Spain). Pre-selected subjects were invited by telephone to an appointment in their primary care centre to be informed about the study. To maximize long-term study participation, individuals were excluded if they had active malignancy, dementia or serious mental illness, had a life expectancy of less than 6 months, were in a palliative care programme, were institutionalized or were frail. Details of the sampling process have been published elsewhere [12]. Among the screened subjects, 40.9% were excluded because they did not meet selection criteria, including willingness to participate. Finally, 278 non-frail community-dwelling elderly subjects were recruited. Recruitment took place from January to July 2014. The hospital research ethics committee approved the study protocol (code 64/13). All participants gave their informed consent by signing a consent form.

### Frailty definition

Subjects were classified as robust, pre-frail or frail according to Fried criteria [9]. Persons were classified as robust, pre-frail or frail if they fulfilled none, 1-2 or  $\geq 3$ , respectively, of the following criteria: a) unintentional weight loss of  $\geq 4.5$  kg in the last 12 months; b) exhaustion, considered to be the case if the subject answered 3 days or more to either or both of 2 questions: "How often in the last week did you feel you could not get going?" and "How often in the last week did you feel that everything you did was an effort?"; c) low physical activity, measured as total weekly physical activity expenditure of  $<383$  kcal in men/ $<270$  kcal in women; d) slow walking speed, measured as  $<0.65$  m/s for a height of  $\leq 173$  cm in men/ $\leq 159$  cm in women or  $<0.76$  m/s for a height of  $>173$  cm in men/ $>159$  cm in women; and e) poor grip strength, measured (using a handheld JAMAR dynamometer) as  $\leq 29$  kg for BMI  $\leq 24$ ,  $\leq 30$  kg for BMI 24.1-28 and  $\leq 32$  kg for BMI  $>28$  in men/ $\leq 17$  kg for BMI  $\leq 23$ ,  $\leq 17.3$  kg for BMI 23.1-26,  $\leq 18$  kg for BMI 26.1-29 and  $\leq 21$  kg for BMI  $>29$  in women. Frailty status was assessed at baseline and at 1-year and 2-year follow-up visits.

### Study factors and data collection

The main study factors included: a) physical exercise, assessed by the International Physical Activity Questionnaire (IPAC) and daily outdoor walking hours; b) nutritional status, assessed by anthropometric measurements (weight, height, BMI), recent weight loss and the short-form Mini Nutritional Assessment (MNA-sf) questionnaire; c) hormones, assessed in terms of fasting plasma levels of total ghrelin, IGF-1, testosterone and insulin; d) inflammatory biomarkers, assessed in terms of plasma levels of interleukin-6 (IL-6) and C-reactive protein (CRP); e) body composition (fat mass, lean mass and muscle mass), assessed by bioimpedance analysis (Bioelectrical Impedance Analyser, EFG3Electrofluidgraph®, Akern SRL); f) fat distribution, assessed by tricipital skinfold, waist and hip circumferences and waist-hip circumference ratio; and g) hand-grip strength, assessed in kg by the handheld JAMAR dynamometer. Other study variables included socio-demographic characteristics; co-morbidities; geriatric syndromes; chronic medication; functional capacity assessed by the Barthel Index, Timed Up-and-Go Test (TUG), unipodal stand test and number of falls; and, finally, a complete blood count (CBC) and basic blood

biochemical analyses for glucose, creatinine (to estimate glomerular filtrate by the MDRD formula), albumin and total cholesterol. Fasting blood samples were taken at 8-9 am. Information on co-morbidities and medication was obtained from the electronic medical records held by the corresponding primary care centres. All other information was obtained directly from the patient by trained healthcare professionals.

### Statistical Analysis

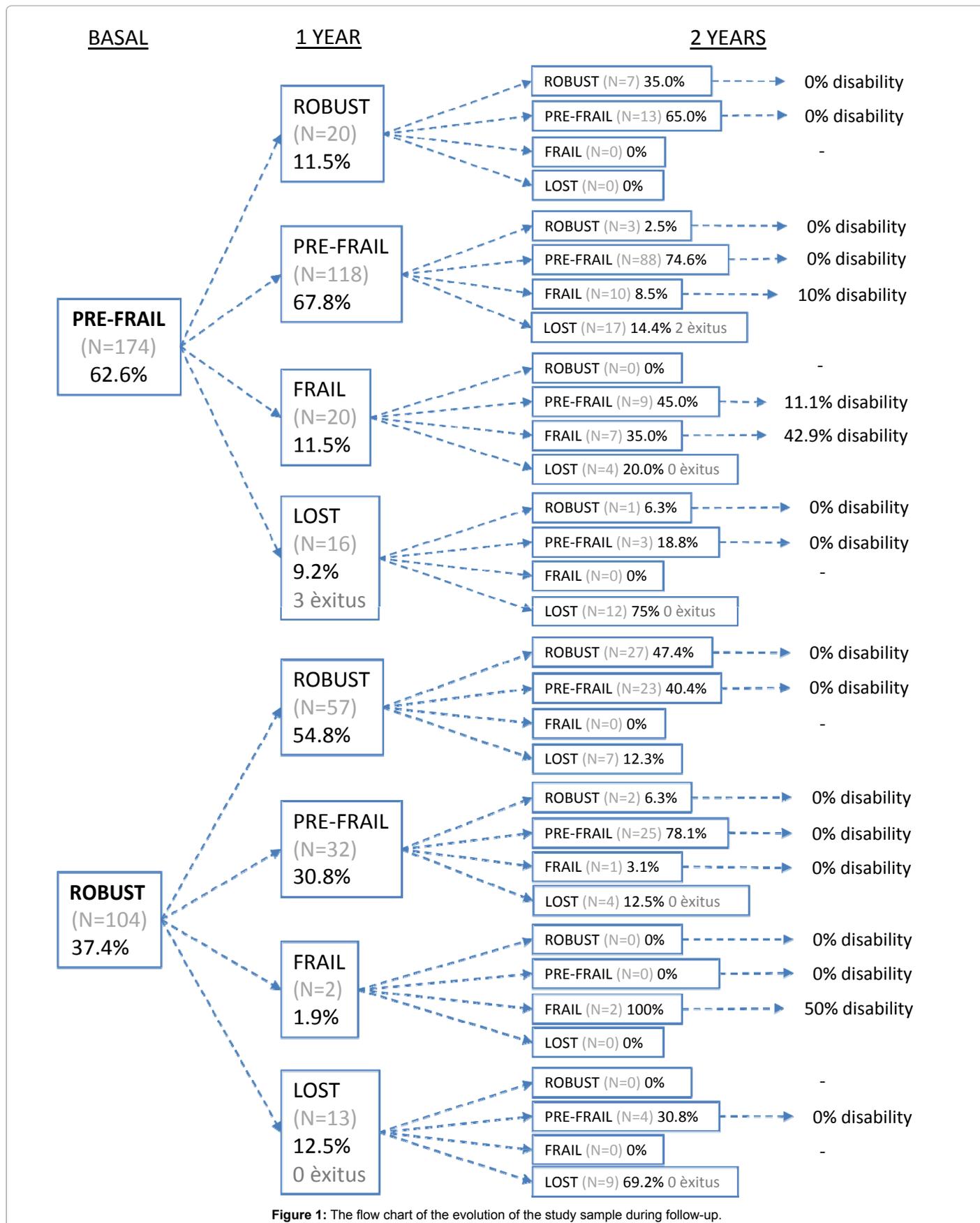
Incidence density of frailty, expressed as the number of new cases of frailty per 100 person-years, was estimated for the overall sample and for robust and pre-frail subgroups. To assess risk factors for frailty, at 2-year follow-up, the robust and pre-frail groups were pooled together in a non-frail group and compared with a frail group. The odds ratios (OR) and their 95% confidence intervals (CI) were used as a measure of association between risk factors and frailty and were calculated using logistic regression. All variables first underwent bivariate analysis, and only variables significantly associated with frailty (for  $P < 0.10$ ) were used to fit a multivariate model. When multicollinearity was detected between variables, only the variable with highest clinical relevance, the highest effect or the variable that allowed the model with the highest goodness of fit was selected. Variables with very few cases in one category were not considered in the multivariate analysis because they would distort the model. All analyses were performed for the overall sample and also separately for men and women to identify possible interactions according to sex that were later tested by logistic regression. A  $p$ -value  $< 0.05$  was considered statistically significant.

### Results

A total of 278 non-frail subjects were recruited, 159 (57.2%) men and 119 (42.8%) women, with a mean age of 79.9 (SD 3.4) years. The mean Barthel score was 98 (SD 4.2) points, the mean number of co-morbidities was 3.3 (1.7), the mean number of medications was 5.3 (2.9) and 96.3% of subjects were considered well nourished. Of the recruited subjects, 53 (19.1%) dropped out during follow-up (7 because of death) and 225 were followed up for 2 years. During this period, 33 non-frail subjects developed a frailty status, which represents an incidence density of 6.8 new cases of frailty/100 person-years. Incidence density was higher in subjects initially classified as pre-frail than in subjects initially classified as robust (10.0 vs 1.6 cases/100 person-year, respectively).

Figure 1 shows the flow chart of the evolution of the study sample during follow-up, reflects the probability of an individual with a specific frailty status (robust, pre-frail or frail) transitioning to another status over the 2-year period. The figure indicates progression from robustness to pre-frailty and frailty, but also reversal of frailty and pre-frailty. Of subjects with a pre-frailty status, 8.2 cases/100 person-year reverted to a robust status.

Table 1 shows the association (in terms of OR and their 95% CI) of socio-demographic variables, co-morbidities and medication with frailty at 2-year follow-up for the overall sample and stratified by sex. It can be observed that being female, arthritis, depression, dyspepsia and number of medications were risk factors for frailty for the overall sample and that the number of co-morbidities was a risk factor for men. Table 2 shows the association of physical exercise, functionality, nutritional status and body composition indicators with frailty at 2-year follow-up for the overall sample and stratified by sex. It can be observed that poor physical activity, impaired balance and functional capacity, BMI and central obesity and loss of muscle mass in the previous year were risk factors for frailty in the overall sample. Table 3 shows the association of different biomarkers and biochemical determinations



Variables	Total (N=225)	Men (N=129)	Women (N=96)
<b>Sociodemographic variables</b>			
Age (years)	1.11 (0.97-1.28)	1.18 (0.90-1.54)	1.08 (0.92-1.28)
Age >80 years	1.87 (0.74-4.72)	2.38 (0.38-14.7)	1.66 (0.55-5.03)
Sex (women)	4.59 (1.61-13.1)	-	-
Live alone	0.38 (0.09-1.72)	-	0.25 (0.05-1.18)
Secondary or higher studies	0.18 (0.02-1.39)	-	0.37 (0.04-3.05)
<b>Comorbidities</b>			
Arthritis	3.41 (1.20-9.74)	2.39 (0.39-14.9)	2.75 (0.72-10.5)
Ischemic heart disease	1.05 (0.33-3.32)	0.88 (0.09-8.20)	1.44 (0.35-5.86)
Peripheral vasculopathy	0.34 (0.04-2.67)	-	0.31 (0.04-2.58)
Stroke	0.66 (0.08-5.27)	3.14 (0.32-31.1)	-
Depression	3.37 (1.24-9.16)	2.52 (0.26-24.6)	2.51 (0.78-8.03)
Chronic bronchitis	0.87 (0.19-3.99)	5.14 (0.79-33.5)	-
Asthma	0.77 (0.10-6.21)	4.83 (0.47-50.2)	-
Diabetes	1.09 (0.34-3.43)	1.28 (0.14-12.0)	0.88 (0.22-3.44)
Gastroesophageal reflux	2.57 (0.78-8.51)	4.83 (0.47-50.2)	1.44 (0.35-5.86)
Chronic kidney failure	0.84 (0.10-6.80)	3.56 (0.36-35.7)	-
Functional dyspepsia	9.85 (2.41-40.3)	-	14.4 (2.35-87.8)
Arterial hypertension	0.94 (0.36-2.47)	-	0.57 (0.19-1.74)
Dyslipidaemia	1.66 (0.65-4.24)	-	0.75 (0.25-2.27)
No. of comorbidities	1.27 (0.98-1.65)	2.27 (1.27-4.06)	1.03 (0.74-1.45)
<b>Medications</b>			
No. of medications	1.31 (1.12-1.54)	1.54 (1.13-2.10)	1.25 (1.01-1.55)
>5 medications	5.65 (1.97-16.2)	7.33 (0.79-67.7)	5.40 (1.57-18.6)
Oral corticoids	0.51 (0.06-4.00)	-	0.64 (0.07-5.55)
NSAIDs	0.71 (0.09-5.67)	5.85 (0.55-62.4)	-
Oral antidiabetics	0.53 (0.12-2.39)	1.28 (0.14-12.0)	0.31 (0.04-2.54)

**Table 1:** Association of baseline sociodemographic variables, comorbidities and medications with frailty at 2-year follow-up for the whole sample and by sex, expressed as OR (95% CI).

Variables	Total (N=225)	Men (N=129)	Women (N=96)
<b>Physical activity</b>			
<500MET (very poor)	1	1	1
500-1000 MET (poor)	0.44 (0.13-1.52)	0.54 (0.04-6.84)	0.40 (0.09-1.70)
1000-1500 MET (moderate)	0.22 (0.06-0.86)	0.16 (0.01-2.91)	0.32 (0.07-1.58)
>1500 MET (vigorous)	0.05 (0.005-0.45)	0.15 (0.01-2.61)	-
<b>Physical activity</b>			
<1000MET (poor)	3.96 (1.46-10.7)	4.14 (0.66-25.9)	2.43 (0.71-8.27)
>1000 MET (vigorous)	1	1	1
<b>Physical examination for functionality</b>			
Outdoor life	0.32 (0.06-1.65)	-	0.34 (0.06-2.04)
Falls in previous 3 months	2.10 (0.23-18.9)	-	1.38 (0.14-13.2)
Unipodal stand test-failed	5.03 (1.94-13.0)	11.8 (1.81-76.7)	2.67 (0.86-8.29)
Timed Up-and-Go test (s)	1.43 (1.16-1.76)	1.14 (0.76-1.70)	1.68 (1.17-2.41)
Peak flow: ≤ 340 L/min (men); ≤ 250 L/min (women)	3.63 (1.31-10.1)	3.75 (0.60-23.4)	2.63 (0.75-9.25)
Barthel Index	0.86 (0.78-0.95)	0.87 (0.71-1.06)	0.87 (0.78-0.99)
Barthel Index <90	6.16 (1.67-22.7)	7.50 (0.68-83.3)	4.81 (0.96-24.2)
<b>Nutritional status</b>			
BMI	1.13 (1.00-1.28)	1.30 (1.01-1.67)	1.04 (0.91-1.19)
BMI ≥ 30	2.12 (0.84-5.40)	2.64 (0.42-16.7)	1.34 (0.44-4.06)
Well nourished (MNA-sf >11)	0.28 (0.05-1.47)	-	1.12 (0.13-10.0)
Tricipital skinfold	1.10 (1.04-1.17)	1.30 (1.07-1.57)	1.05 (0.96-1.14)
Waist/hip ratio: men>1; women>0.9	3.83 (1.46-10.0)	1.82 (0.19-17.4)	2.23 (0.58-8.56)
<b>Body composition</b>			
Fat mass (% total body weight)	1.07 (1.01-1.13)	1.05 (0.95-1.16)	1.01 (0.92-1.11)
Fat mass >percentile 25	4.08 (0.92-18.1)	-	3.50 (0.74-16.6)
Muscular mass (% total body weight)	0.88 (0.81-0.96)	0.93 (0.78-1.11)	0.92 (0.79-1.07)
Fat free mass (% total body weight)	0.92 (0.86-0.98)	0.87 (0.71-1.07)	0.99 (0.90-1.09)
Muscle mass index	0.79 (0.58-1.08)	1.49 (0.82-2.70)	0.87 (0.56-1.36)
Muscle mass index >percentile 25	0.92 (0.32-2.65)	1.57 (0.17-14.6)	0.53 (0.15-1.91)
Muscle mass loss >10% in last year	4.86 (1.33-17.8)	5.5 (0.49-61.2)	3.90 (0.80-18.9)

**Table 2:** Association of baseline physical exercise, functionality, nutritional status and body composition with frailty at 2-year follow-up for the whole sample and by sex, expressed as OR (95% CI).

Variables	Total (N=225)	Men (N=129)	Women (N=96)
<b>Complete blood count</b>			
Anaemia	2.08 (0.64-6.78)	2.33 (0.24-22.6)	1.78 (0.43-7.40)
Haematocrit (%)	0.83 (0.73-0.95)	0.93 (0.70-1.24)	0.87 (0.73-1.04)
Leucocytes (× 10 <sup>9</sup> /uL)	1.04 (0.92-1.18)	1.03 (0.84-1.26)	1.14 (0.89-1.46)
Platelets (× 10 <sup>9</sup> /uL)	1.00 (0.99-1.01)	0.99 (0.97-1.01)	0.99 (0.99-1.01)
<b>Biochemical, hormonal and inflammatory biomarkers</b>			
Total cholesterol (mg/dL)	1.02 (1.00-1.03)	1.02 (0.99-1.04)	1.01 (0.99-1.03)
Total cholesterol >200 mg/dL	2.47 (0.95-6.45)	2.46 (0.40-15.3)	1.95 (0.61-6.22)
Glucose (mg/dL)	0.98 (0.96-1.01)	0.94 (0.86-1.03)	0.99 (0.97-1.02)
Glucose ≥ 115 mg/dL	0.52 (0.15-1.84)	-	0.82 (0.21-3.20)
Glomerular filtrate <60	7.54 (2.87-19.8)	-	3.85 (1.21-12.3)
Albumin (mg/dL)	1.01 (0.14-7.26)	1.13 (0.02-52.4)	1.87 (0.17-20.9)
Albumin ≤ 4 mg/dL	1.48 (0.17-12.7)	10.0 (0.84-118.5)	-
Total ghrelin (pg/mL)	1.00 (1.00-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
Total ghrelin (cat P25): >839(men); >1033(women)	1.30 (0.42-4.07)	0.48 (0.08-3.00)	2.17 (0.45-10.4)
Testosterone (ng/mL)	0.71 (0.55-0.91)	0.80 (0.47-1.36)	0.92 (0.19-4.34)
Testosterone:>3.59(men); >0.10(women)	0.69 (0.25-1.89)	0.44 (0.07-2.78)	0.81 (0.23-2.86)
Insulin (mcIU/mL)	1.01 (0.96-1.05)	1.00 (0.93-1.08)	1.06 (0.94-1.19)
Insulin: <6(men); <5.5(women)	0.90 (0.33-2.46)	-	1.73 (0.55-5.42)
Possible insulin resistance (HOMA>3)	1.01 (0.84-1.22)	0.74 (0.08-6.90)	3.78 (1.05-13.6)
IGF-1 (ng/mL)	0.99 (0.98-1.01)	0.98 (0.96-1.01)	1.01 (0.99-1.02)
IGF-1: >92 (men); >77(women)	0.53 (0.20-1.41)	0.08 (0.01-0.72)	1.02 (0.26-4.03)
Cortisol (µg/dL)	1.08 (0.98-1.20)	0.87 (0.69-1.10)	1.16 (1.01-1.34)
Cortisol (>14.5)	2.43 (0.69-8.61)	0.65 (0.10-4.02)	6.00 (0.75-48.2)
CRP (pg/mL)	1.91 (0.42-8.66)	2.29 (0.23-23.3)	1.50 (0.15-15.1)
CRP (≥ 0.8)	1.72 (0.20-15.1)	-	5.69 (0.34-96.8)
TNF-alpha (pg/mL)	1.14 (0.93-1.39)	0.99 (0.67-1.48)	1.24 (0.96-1.60)
TNF-alpha: <8.5(men); <7.7(women)	1.08 (0.36-3.19)	2.00 (0.31-12.8)	0.75 (0.17-3.31)
IL-6 (pg/mL)	1.01 (0.98-1.04)	1.01 (0.97-1.05)	1.08 (0.98-1.19)
IL-6:< 3(men);< 2.4(women)	0.08 (0.01-0.60)	-	0.15 (0.02-1.24)

**Table 3:** Association of baselinebiomarkers with frailty at 2-year follow-up for the whole sample and by sex, expressed as OR (95% CI).

<b>Overall sample<sup>(1)</sup></b>		
Variables	OR (95%CI)	P
Depression	6.06 (1.26-30.0)	0.027
Number of medications	1.49 (1.17-1.90)	0.001
Waist/hip ratio: men>1; women>0.9	5.44 (1.24-23.9)	0.025
Muscle mass loss>10% in the last year	12.1 (1.66-88.6)	0.014
Cholesterol>200 mg/dL	9.76 (1.84-51.9)	0.008
Glomerular filtrate <60	10.2 (2.22-46.9)	0.003
IL-6: men<3; women<2.4	13.9 (1.33-145.0)	0.028
<b>Men<sup>(2)</sup></b>		
No. of co-morbidities	2.75 (1.25-6.01)	0.011
IGF-1>92 ng/dL	0.045 (0.003-0.65)	0.023
<b>Women<sup>(3)</sup></b>		
No. of medications	1.34 (1.06-1.68)	0.012
Cortisol (µg/dL)	1.17 (1.02-1.33)	0.020

(1) Variables included in the model (STEPWISE): sex, arthritis, depression, number of medications, poor physical activity (<1000 MET), waist/hip ratio, muscle mass loss >10% in the last year, cholesterol >200 mg/dL, MDRD (<60), IL-6 (men<3; women<2.4), testosterone (ng/ml).

(2) Variables included in the model (STEPWISE): number of co-morbidities, BMI, IGF-1>92 ng/dL, poor physical activity (<1000 MET).

(3) Variables included in the model (STEPWISE): number of medications, cortisol, IL-6<2.4 pg/mL, poor physical activity (<1000 MET)

**Table 4:** Results of the multivariate analysis results for risk factors for frailty.

with frailty. It can be observed that a glomerular filtrate <60 and low levels of testosterone or IL-6 were risk factors for frailty in the overall sample, that a low IGF-1 level was a risk factor for men and that insulin resistance and high levels of cortisol were risk factors for women.

However, no significant interactions between study factors and gender have been detected.

Finally, Table 4 presents the results of the multivariate analysis, for the overall sample and separately for men and for women. It can be observed that depression, number of medications, central obesity, muscle loss, high levels of total cholesterol and IL-6 and a glomerular filtrate <60 were independent risk factors for frailty. The number of co-morbidities and IGF-1 levels showed an independent effect in men, and the number of medications and cortisol levels showed an independent effect in women. No significant interactions were observed between inflammatory, hormonal and nutritional factors in their impact on frailty development.

## Discussion

The results of this study indicate the following: a) that frailty incidence is approximately 7 new cases per 100 person-years in community-dwelling subjects ≥ 75 years old; b) that frailty and pre-frailty are reversible states; c) that the main potentially modifiable or treatable frailty risk factors are certain co-morbidities, number of medications, low physical activity, poor functionality, central obesity, loss of muscle mass and high levels IL-6; and, finally, d) that there is no conclusive evidence of differences in frailty risk factors for men compared to women.

Although several studies have reported the prevalence of frailty in different populations (2), there are very few studies that report frailty incidence rates. The results of this longitudinal study indicate that 6.8% of community-dwelling non-frail subjects ≥ 75 years become frail each

year. As would be expected, most of these frail persons (94%) transition from a previous pre-frailty status, leaving only 6% to transition directly from a robust status. Data from this study also indicates that frailty and pre-frailty were both reversible and, taking losses into account, resulted in stabilization of the frailty prevalence rate at 8.8% at the end of the first and second years of follow-up.

It has been reported that frailty increases the risk of disability and dependency [4], thereby increasing healthcare burden and costs [5,6]. Prevention or reversal of this clinical condition must be based on the removal of modifiable risk factors or on the introduction of factors or interventions that have been demonstrated to have a protective effect. To date, only multi-component exercise programmes-including aerobic activity, strength exercises and flexibility have demonstrated to prevent or reverse frailty [13-15]. Different systematic reviews and meta-analyses have concluded that physical activity is a crucial way to maintain or improve strength, function and mobility in frail older adults [16]. The results of our study corroborate current scientific evidence regarding the protective effect of physical exercise, which may reduce frailty by decreasing muscle inflammation, increasing anabolism and providing stimuli for muscle synthesis [17].

Regarding risk factors for frailty, our study has linked certain socio-demographic characteristics, clinical conditions, nutritional and body composition parameters and blood biomarkers with the occurrence of new cases of frailty. Because of the longitudinal and prospective design of the study, there is no temporal ambiguity between these study factors and frailty.

The fact that the women in our study showed an increased risk of frailty in the bivariate analysis corroborates results from other studies reporting a higher prevalence of frailty in women in cross-sectional studies [2,18]. However, this effect disappeared when adjusted for other variables such as arthritis, depression, number of medications, physical activity, abdominal obesity and certain blood biomarkers, thereby undermining a genuine female-sex effect.

Regarding co-morbidities, we identified arthrosis, depression, functional dyspepsia and the number of medications as risk factors for frailty in the bivariate analysis. We interpret the effect of arthritis to be a consequence of limited physical activity secondary to pain, a highly prevalent clinical condition in the elderly population [18] and a possible trigger of the frailty process. Depression has been reported elsewhere as a contributor to frailty [19,20]. Frailty in depressed subjects may be a consequence of a socially less active life, limited outdoor activity, reduced mobility, lower food intake and unhealthy habits. A lesser known risk factor for frailty is dyspepsia, present in a relatively small percentage of our study sample (<4.7%) and unevaluable in the multivariate models. Dyspepsia symptoms may be associated with impaired gastric motility and acid secretion [21] and with gastrointestinal inflammation. Although other studies have reported more gastrointestinal problems in frail subjects than in pre-frail or robust patients [12,22], the fact that little is known about this relationship would indicate that further studies are necessary. Finally, regarding the number of medications, this reflects the patient's comorbidity burden (more medications indicate more co-morbidities). The accumulation of diseases and other clinical deficits is very much part of the very concept of frailty [8,22]; nonetheless, since, in our study, the number of medications showed an independent effect in the multivariate model, the possibility cannot be ruled out that certain medications or drug interactions could predispose individuals to frailty [23].

In relation to obesity and adiposity, we observed a crude effect for both a high waist/hip ratio and the tricipital skinfold, but did not observe any significant effect of a BMI>30. Abdominal obesity was maintained as a significant risk factor for frailty in the multivariate analysis - a result that agrees with the relationship between obesity and poor physical activity and weakness reported by other studies [24]. Growing evidence suggests that obesity, and especially abdominal obesity, may contribute to frailty by promoting pro-inflammatory processes, insulin resistance, fat infiltration of the skeletal muscle and hormonal changes (such as increased leptin or decreased adiponectin levels) with catabolic and satiation effects [24-26]. These changes may lead to a loss of muscle mass and the development of sarcopenic obesity and frailty. Abdominal obesity is a component of the metabolic syndrome and is associated with insulin resistance, both of which have been associated with an increased risk of frailty [27]. Although total cholesterol did not acquire significance in the bivariate analysis, the multivariate model showed that levels >200 mg/dL were an independent risk factor for frailty. The effect of dyslipidaemia may be related with the previously mentioned effect of the complex obesity-metabolic syndrome but needs to be further studied. On the other hand, a low glomerular filtrate rate was also shown to have an independent effect on frailty in our study. Our result indicating that kidney failure was a risk factor for frailty also agrees with results reported by other authors [22]. Some evidence suggests that age-related changes in the immune system, such as a declining immune function (immunosenescence) or a state of chronic inflammation (inflammaging), may contribute to sarcopenia and frailty [28]. Our result regarding an association between high levels of baseline IL-6 and 2-year follow-up frailty corroborates other studies indicating that activated inflammation is a characteristic of the frailty syndrome [29,30].

During ageing, a gradual decline in GH and IGF-1 production called "somatopause" - is associated with multiple anabolic hormone deficiency and has been implicated in the development of sarcopenia and frailty [31]. It has been reported that higher levels of serum IGF-1 is independently associated with more muscle mass and better handgrip performance in both sexes [32]. However, IGF-1 is a sensitive nutritional marker rather than just an anabolic hormone and is negatively influenced by poor mineral and overall nutritional states and subclinical low-grade inflammation [31]. Although our study has shown a protective effect of high levels of IGF-1 only in men, no significant interaction was observed between IGF-1 and sex, suggesting that the lack of a significant effect in women could be due to the cut-off point used and/or to poor statistical power. Regarding cortisol, we observed that higher levels of cortisol were a risk factor for frailty in women. Johar et al. [33] reported that frailty is associated with blunted cortisol reactivity, with lower morning and higher evening salivary levels. Ageing is accompanied by an imbalance between anabolic and catabolic hormones, but the relationship between any single hormonal derangement and frailty is still not well established. That said, multiple hormone dysregulation has been described as a powerful marker of frailty and mortality in both men and women [34,35], indicating that frailty increases as the number of hormonal dysregulations increases.

A major strength of our study is undoubtedly its longitudinal design. As for limitations, sample size was relatively small, and the follow-up period was short in terms of obtaining a sufficient number of new frailty cases to guarantee enough statistical power (for low-prevalence risk factors, risk factors weakly associated with frailty and for multivariate analyses). Additionally, as with all longitudinal studies, losses to follow-up and dropouts are a major inconvenience when analyzing and interpreting data. In our study, the fact that 19%

of the recruited sample was lost over the follow-up period may have led to underestimating frailty incidence, although we are of the opinion that these losses did not bias the relationships between study factors and frailty. Finally, although the Fried criteria have become a standard for the diagnosis of frailty in clinical research, we would potentially question its reliability for patients with values for weight loss, strength, exhaustion, physical activity and gait speed that are very close to the cut-off points. Small accidental variations in these values may result, for instance, in different frailty status classifications and may even partially explain transitions from one frailty status to another.

## Conclusion

This study describes a relatively high incidence of frailty in community dwelling subjects aged  $\geq 75$  years, but also shows that frailty and pre-frailty are reversible conditions. The study has also identified some risk factors for frailty, mostly associated with inflammation, obesity and certain co-morbidities. No significant sex-related differences in risk factors were identified. Our results suggest that good control over underlying diseases, pain and body weight and the promotion of physical activity may contribute to reducing inflammation and to preventing frailty in elderly patients. The studied factors only explain a small part of frailty occurrence, so further research is needed to identify other risk factors for frailty and to deeply understand the role of some known factors such as pain, depression or medications. Moreover, there is also a need for well-designed and powered clinical trials assessing the effectiveness of interventions aimed to reduce the incidence of frailty syndrome.

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The authors declare that they have no conflict of interest in relation with this project.

## Ethical Standards

The study complies with the current Spanish law. The local ethical committee approved the study protocol (CEIC CSdM 64/13). All participants gave their informed consent by writing.

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