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THE PREVALENCE OF FRAILTY SYNDROME IN AN OLDER POPULATION FROM SPAIN. THE TOLEDO STUDY FOR HEALTHY AGING

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Abstract: *Objective:* To assess the prevalence of the frailty syndrome and its associated variables among the older adult population in the province of Toledo (Spain). *Methods:* Data were taken from the Toledo Study for Healthy Aging, a population-based study conducted on 2,488 individuals aged 65 years and older. Study participants were selected by a two-stage random sampling from the municipal census of Toledo, covering both institutionalized and community dwelling persons from rural and urban settings. Data were collected from 2006 to 2009, and included information on social support, activities of daily living, comorbidity, physical activity, quality of life, depressive symptoms, and cognitive function. In addition, a nurse collected anthropometric data, conducted tests of physical performance (walk speed, upper and lower extremities strength, and the stand-and-sit from a chair test) and obtained a blood sample. The diagnosis of the frailty syndrome was based on the Fried criteria (weakness, low speed, low physical activity, exhaustion, and weight loss). *Results:* In total, 41.8% (95% confidence interval [CI] 39.4-44.2%) of the study participants were prefrail, and 8.4% (95% CI 7.1-9.8%) were frail. There were no differences in the prevalence of frailty by sex, level of education, occupation, marital status, or place of residence. The frequency of the frailty syndrome increased with age, and was higher in those with disability, depression, hip fracture and other comorbidity, such as cardiovascular disease and disorders of the central nervous system. *Conclusions:* The prevalence of the frailty syndrome in older Spanish adults is high and similar to that reported in other populations in the Mediterranean basin.

Key words: Frailty, prevalence, elderly, cross-sectional study.

Background

Many studies have shown a direct relationship between disease and disability, but have not yielded a sufficient explanation for disability in the absence of disease or for the great variability in aging. Frailty is an emerging concept which could provide the conceptual framework to fill this gap. There are at least two ways to approach the concept of frailty (1). The first one understands frailty as a result of several aging-related deficits that will lead to poor health in the short-medium term. An example of this approach is the Rockwood Frailty Scale that includes 40 deficits that predict frailty (2). The second approach understands frailty as a group of signs and symptoms that share the same pathologic origin and that progress over time. A paradigm of this approach is the model developed by Walston and Fried (3). They identified clinical signs of frailty such as weight loss, sarcopenia, low physical activity and weakness, and they suggested procedures to measure them. They also proposed the concept of frailty cycle, in which chronic inflammation and neuro-endocrine imbalance lead to sarcopenia and low physical activity causing a decrease in the energy requirements as well as altered metabolism.

The impact of the frailty syndrome (FS) worsens with age (3); moreover the FS is associated with cardiovascular risk factors and vascular disease (3-6). In longitudinal studies, frailty has also been found to be a risk factor for mortality, disability and hospitalization (3, 7-9). Despite all these data, further research is required to characterize the frailty phenotype (10, 11). In particular, only a few studies on this topic have been conducted on populations from the Mediterranean basin, whose very long life-expectancy and characteristic lifestyles (psychosocial factors, sun exposure, food consumption and open-air physical activity) may influence the frequency and variables associated to the FS.

The Toledo Study for Healthy Aging (TSHA) was set to assess the frequency of FS in the older adult population of Spain, and to examine its underlying mechanisms, risk factors, clinical and functional significance, and its impact on the health care system. In this paper, we report the prevalence of the FS, and its associated factors, among the older adult population in the province of Toledo (Spain).

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Methods

Study design and participants

Data were taken from the baseline assessment in the TSHA, a population-based longitudinal study of institutionalized and community dwelling individuals aged 65 years and over, residing in the province of Toledo. The TSHA is composed by two cohorts. The first one, called the historic cohort, is formed by the survivors of a previous study (theToledo Study) among persons aged 77 and older (12). The second cohort, called the new cohort, was formed by individuals 65-76 years of age who just joined the study. Subjects from both cohorts were selected by a two-stage random sampling of the municipal census of the province of Toledo (13). Sampling was conducted within census sections in six strata according to sex, age and town-size groups. The study sample comprised 24% of the population aged 65 and older living in the province of Toledo. We found 1,560 of the survivors from the Toledo Study to be eligible for the historic cohort, and 4,342 persons for the new cohort. Selection of study participants, and data collection at baseline, were conducted from June 2006 to September 2009.

Signed informed consent was obtained from all participants. The study was approved by the Clinical Research Ethics Committee of the Toledo Hospital.

Data collection

We collected data in three stages. In the first one, 6 psychologists conducted computed assisted interviews, performed face-to-face at the subjects' home. The average duration of the interview was 90 minutes. The questionnaires included socio-demographic data, social support, activities of daily living, health-related quality of life, comorbidity, physical activity, diet, tobacco and alcohol consumption, depressive symptoms and an extensive neuropsychology assessment.

In the second stage, three nurses did a physical examination and performed some clinical tests at subjects' homes. The average duration of this stage was 60 minutes per study participant. Nurses ascertained heart rate, blood pressure, and anthropometry. Also, they performed electrocardiograhy, an spirometry test, a determination of the ankle-brachial index, and a physical performance test (upper and lower extremity strength, walk speed, balance and a sit-and-stand from chair test). The orientation and movement acceleration tests of the physical performance were evaluated with an inertial Orientation Tracker MTx (XSENS, Xsens Technologies B.V.Enschede, Netherlands) attached over the L3 region. Nurses also assessed cognition and asked about urinary incontinence.

Both the psychologists and nurses were trained specifically for this study, and were certificated before they started field work.

In the third stage, study participants went to their health center to provide a fasting blood sample while fasting. Within two hours, samples were taken in containers at 2-4 ºC to the laboratory, where they were separated in aliquots and stored at -80ºC. White blood cells were isolated from some samples and freeze in liquid nitrogen.

Measures

Frailty syndrome

The diagnosis of frailty was based on the criteria by Fried et al (3):

Weakness: defined as the worse quintile of maximum strength on the dominant hand adjusted for sex and body mass index (kg/m^2). Strength was measured with a Jamar hydraulic dynamometer, according to the standards of the Hispanic EPESE (14). Weight was measured with a SECA precision scale, and height with a stadiometer on a wall without skirting board.

Low energy: subjects were classified as having "low energy" when they provided a positive answer to any of the following two questions from the CES-D (Center for Epidemiologic Studies Depression Scale) (15): "I felt that anything I did was a big effort" and "I felt that I could not keep on doing things" at least 3 to 4 days a week".

Slowness: defined as the worse quintile in the three-meter walking speed test, adjusted for sex and height according to the standards of the Short Physical Performance Battery (16).

Low physical activity: defined as the worse quintile in the PASE score (17).

Weight loss: defined as unintentional weight loss of 4.5 kg or more in the last year.

We assigned 1 point to each variable, and built an score as the sum of points for all them. According to this score, subjects were classified as non-frail (0 points), pre-frail (1-2 points) and frail (3-5 points). We excluded subjects who could not perform the physical performance test battery due to poor health.

Comorbidity

Data were also collected on comorbidity, from medical diagnoses and the information given by the own subject. We considered ischemic heart disease, peripheral vascular disease, stroke, syncopal episodes, hypertension, diabetes, high cholesterol, chronic obstructive pulmonary disease-COPD, peptic ulcer disease, fractures, osteoporosis, osteoarthritis, cancer, dementia, Parkinson disease, renal, thyroid and liver disease. We also assessed limitations in basic (Katz index) (18) and instrumental (Lawton index) (19) activities of daily living, depressive symptoms (15 items Yesavage s Geriatric Depression Scale) (20), and cognitive status (Mini-Mental State Examination). The cut-offs for cognitive impairment varied with educational level: 17/18 for illiterates, 20/21 for those who attended school and 23/24 for those with higher level of education (21, 22).

Statistical analysis

We calculated the prevalence of FS and its 95% confidence interval (CI) for the whole sample, and for subgroups defined by age, sex, comorbidity and disability. The chi-square (X2)

test was used to assess differences in proportions, and the Student T test or the Mann-Whitney test, as appropriate, to assess differences in means. To test for a linear gradient in proportions we used the chi-square for trend.

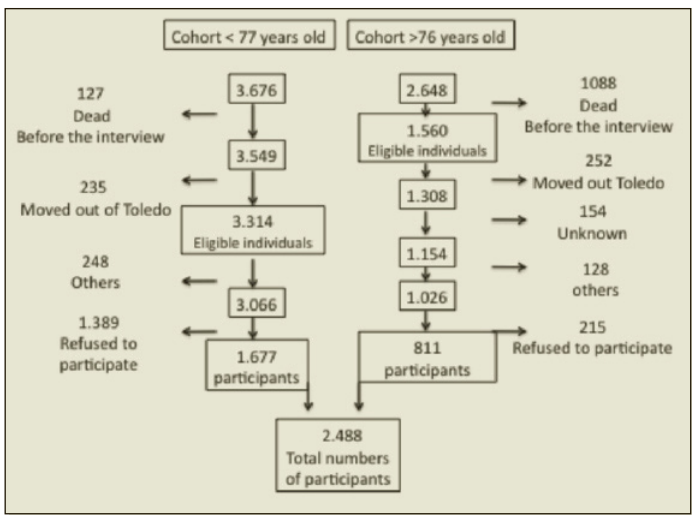
We set the statistical significance at two-sided p <0.05. Statistical analyses were performed with Stata version 9.2 and SPSS version 15.0.

Results

Study sample

From the 4,242 individuals 65 to 76 years old selected to participate in the new cohort of the TSHA, 566 could not be contacted due to errors in the municipal census. 127 died before the interview, and 235 had moved from Toledo. Therefore, 3,066 individuals were invited to participate in the study, and 1,667 agreed (62.3%) (Figure 1).

Figure 1
Flow of participants in the Toledo Study for Healthy Aging (N= 2,488)



Of the 1,560 subjects over 77 years of age from the Toledo Study who were still alive, 154 could not be found, 258 had moved out of Toledo, and 215 refused to participate. As a result, the historic cohort comprised 811 subjects (Figure 1).

Thus, the final sample of the TSHA consisted of 2,488 individuals aged 65 years and older. All of them participated in the interview corresponding to the first stage of the study, 1,972 participated in the physical examination, and 1,752 gave a blood sample. Study participants had a lower proportion of young-old (65-69 yrs) and old-old individuals (> 84 yrs.) than the population of Toledo (18.7% vs. 23.4% and 8.3% vs. 13.1% respectively).

The participants mean age was 75.2 years (standard deviation 6.2); 56.1% were women and 64% lacked formal schooling. Only 1.9% was institutionalized. We found no significant differences in the socio-demographic or clinical characteristics between the participants in the three stages of data collection (table 1).

Table 1
Characteristics of the participants in the Toledo Study for Healthy Aging, by type of information provided by the participant

	Interview (N= 2,488) n (%)	Physical exam (N=1,972) n (%)	Blood sample (N= 1,751) n (%)
Age (years)			
65-69	466 (18.7)	358 (18.2)	329 (18.8)
70-74	754 (30.3)	588 (29.8)	535 (30.5)
75-79	721 (29.0)	593 (30.1)	535 (30.5)
80-84	339 (13.6)	286 (14.5)	232 (13.2)
>84	208 (8.4)	147 (7.5)	121 (6.9)
Sex			
Males	1092 (43.9)	853 (43.3)	748 (42.7)
Females	1396 (56.1)	1119 (56.7)	1004 (57.3)
Educational level			
No formal schooling	1602 (64.4)	1294 (65.6)	1181 (67.4)
Uncompleted school	444 (17.8)	350 (17.7)	305 (17.4)
Primary or secondary school	192 (7.7)	149 (7.6)	129 (7.4)
High school and more	224 (9.0)	161 (8.1)	128 (7.3)
Marital status			
Single	156 (6.3)	109 (5.5)	108 (6.2)
Married	1705 (68.5)	1391 (70.5)	1233 (70.4)
Widow	597 (24.0)	454 (22.0)	393 (22.4)
Other	27 (1.0)	18 (0.9)	17 (1.0)
Years of schooling, mean (SD) (SD)	5.3 (12.3)	5.20 (12.3)	4.9 (11.6)
Heart attack	148 (6.0)	122 (6.2)	109 (6.2)
Angina	155 (6.2)	122 (6.2)	109 (6.2)
Claudication	28 (1.1)	22 (1.1)	22 (1.3)
Heart failure	123 (5.0)	92 (4.7)	82 (4.7)
Hypertension	1208 (48.6)	972 (49.4)	866 (49.4)
Diabetes	482 (19.4)	382 (19.4)	333 (19.0)
Stroke	141 (5.6)	112 (5.6)	96 (5.4)
Parkinson's disease	56 (2.3)	42 (2.1)	33 (1.2)
COPD	142 (5.7)	108 (5.5)	89 (5.1)
Dementia	53 (2.1)	36 (1.8)	29 (1.7)
Tumor	159 (6.4)	116 (5.9)	107 (6.1)
Hip fracture	73 (2.9)	55 (2.8)	54 (3.1)
Limitation in BADL	504 (20.5)	401 (20.6)	340 (19.4)
Limitation in IADL	1426 (62.8)	1138 (62.4)	996 (61.8)
Cognitive impairment	418 (16.8)	319 (16.2)	276 (15.8)
Depression (GDS > 4)	399 (16.0)	329 (16.7)	280 (16.0)

SD = standard derivation: COPD = chronic obstructive pulmonary disease; BADL = basic acitivities of daily living; IADL = instrumental activities of daily living; GDS= geriatric depression scale.

Frailty syndrome and associated variables

The prevalence of each criterion of the FS was 20.4% for weakness, 24.1% for slowness, 19% for low physical activity, 8.5% for weight loss, and 12.5% for low energy. For some criteria, there were significant differences between men and women: low activity (27.7% vs. 12.2%; p<0.001), weight loss (5.9% vs. 11%; p<0.001) and low energy (5.3% vs. 18.5%; p<0.001).

According to the criteria by Fried et al (3), 41.8% (39.4%-44.2%) (n=687) of the subjects in the cohort were prefrail, and 8.4% (7.1%-9.8%) (n=138) were frail. There was no difference between sexes, but the frequency of FS increased with age, reaching a prevalence of 27.3% in those older than 84 years (figure 2). There was no difference in the prevalence of FS by educational level, marital status or place of residence (Table 2).

We found FS to be associated with vascular disease (stroke,

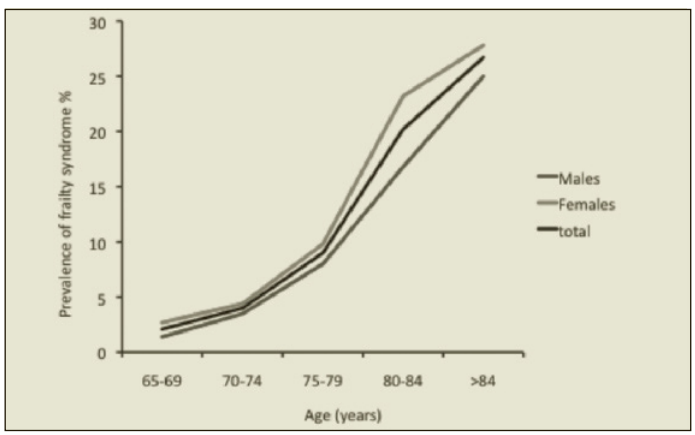
ischemic heart disease, peripheral vascular disease), but no association was observed with cardiovascular risk factors such as diabetes, hypertension and high cholesterol. There was also a strong association between FS and disorders of the central nervous system, such as Parkinson s disease, dementia, cognitive impairment, and depression. Moreover, FS was also more frequent in those with chronic obstructive pulmonary disease or hip fracture in the past. Lastly, FS was more common in those with limitations in basic or instrumental activities of daily living (table 3).

Table 2
Prevalence (%) of frailty syndrome by socio-demographic variables in the Toledo Study for Healthy Aging

	% (95% CI)	P value
Age (years)		P < 0.001
65-69	2.1 (0.8-4.3)	
70-74	4.0 (2.5-6.1)	
75-79	8.9 (6.5-11.8)	
80-84	20.1 (15.0-26.2)	
>84	27.3 (18.2-38.2)	
Sex		NS
Males	7.7 (5.4-9.4)	
Females	9.3 (7.5-11.3)	
Occupation:		NS
White collar	5.4 (3.0-8.7)	
Blue collar	7.0 (3.7-12.0)	
Non qualified workers	8.4 (6.4-10.8)	
House wifes	10.0 (7.6-12.8)	
Marital status		NS
Single	11.8 (6.0-20.1)	
Married	7.4 (5.9-9.0)	
Widow	10.9 (7.8-14.7)	
Other	6.6 (0.1-31.9)	
Educational level		NS
None	8.6 (7.0-10.5)	
Uncomplete school	9.8 (6.6-13.9)	
School and more	6.1 (3.6-9.6)	
Place of residence		NS
Rural	8.3 (6.7-10.3)	
Urban	8.4 (6.4-10.8)	

CI: Confidence interval; NS: not significant.

Figure 2
Prevalence of frailty syndrome by sex and age in the Toledo Study for Healthy Aging



Discussion

The TSHA is the first to determine the prevalence, distribution and biologic associations of FS in the elder population from Spain. Important characteristics of the TSHA are that it was conducted in a Mediterranean country where studies on FS are scarce (23), and that the FS was diagnosed according to pre-determined and validated criteria. Moreover, the TSHA covered both urban and rural settings which differ in terms of sociodemographics and lifestyle. We enrolled 50% of the eligible population which is a figure similar to that reported in other studies in Europe (23). We observed that those individuals who refused to participate were younger and lived in the urban setting but we do not have more data about them because they refuse to cooperate in the collection of any data. The percentage of rejection was higher than a previous population-based study (20%) conducted on the same geographic area in 1994. The causes of this high percentage of rejection is known but one possible explanation could be related with sociodemographical changes occurred in the last years. This study shows that the FS, defined with the criteria by Fried et al (3), has a high prevalence in the older adult population of a Mediterranean country. When we extrapolated this results to the elderly population from Toledo, the prevalence of frailty was 8.9%, which is similar to that in other studies using comparable methods (3, 5, 24, 25) but lower to those in the United States of America (7, 26) or in the Share Study (23). This latter study, which covered 816 Spanish subjects over 65 years of age, reported a prevalence of frailty of 27.3%, three times higher than ours. One possible reason for this discrepancy is the different procedure used in The Share Study to assess the Fried criteria In general, the Share Study found a higher frequency in frailty that in other studies conducted in Mediterranean countries. This is the case for France (the Three Cities Study) (8), and Italy (The Inchianty Study) (5) where the prevalence of Frailty was 7% and 8.8% respectively (very similar to the results we obtained in Spain), and lower than the results obtained for France and Italy in The Share Study (15% and 23% respectively).

In our study the FS increased with age. FS was 13 times more prevalent among individuals over 84 years of age compared to those between 65 and 69. There is almost an exponential increase of frailty with age, as shown in other studies (3). We found no difference in the prevalence of FS between sexes (3, 23), though it might be due to the fact that some criteria were adjusted for sex. Of note is the lack of significant association between FS and education, occupation, and place of residence, even though these factors influence lifestyle and, thus, could influence frailty.

Our findings are similar to the results from previous studies suggesting that frailty is strongly associated to disability (table 3), but they are not the same because 68% and 87% of the subjects who had some dependency to basic and instrumental activities of daily living were not frail (3, 4, 8, 27, 28). As in previous studies, frailty was strongly associated with comorbidity, especially symptomatic cardiovascular diseases (29) and cognitive impairment. This latter association has been found in so many studies (3, 10,11,28, 30, 31) that cognitive impairment has been proposed as part of the frailty phenotype (1, 31). The TSHA shows that this association is reciprocal

since individuals with cognitive impairment have a high prevalence of frailty and frail individuals have even a higher prevalence of cognitive impairment. This could be explained by the strong association between FS and cardiovascular disease, but recent work has shown that frail subjects are at higher risk for Alzheimer s disease with worse pathologic changes in the brain (31, 32). Lastly we observed that depression (Geriatric Depression Scale > 4) was present in 46.5% of the frail subjects. This strong association makes sense since one of the frailty criteria, exhaustion, is part of the diagnostic criteria for depression.

Table 3
Frailty prevalence according to comorbidity

Comorbidity	Prevalence of frailty		p value
	Present (95% CI)	Absent (95% CI)	
Ischemic heart disease	15,1 (10,2-21,3)	7,5 (6,4-8,9)	P <0,001
Peripheral vascular disease	21,0 (6,0-45,5)	8,0 (6,7-9,4)	NS
Heart failure	11,7 (5,2-21,8)	8,2 (6,8-9,6)	NS
Hypertension	8,4 (6,6-10,5)	8,2 (6,4-10,4)	NS
Diabetes	10,2 (7,1-14,1)	7,8 (6,4-9,4)	NS
Stroke	23,9 (14,6-35,5)	7,7 (6,4-9,1)	P <0,001
Parkinson's disease	42,8 (21,8-65,9)	7,9 (6,6-9,3)	P <0,001
Dementia	33,3 (13,3-59,1)	7,9 (6,6-9,3)	P <0,001
COPD	21,5 (13,6-31,2)	7,9 (6,6-9,39)	P <0,001
Hypercholesterolemia	7,72 (5;7-10,1)	8,8 (7,1-10,8)	NS
Atrial fibrilation	20,0 (10,0-33,7)	7,8 (6,5-9,3)	P <0,01
Hip fracture	33,3 (19,0-50,2)	7,75 (6,4-9,1)	P <0,001
Dependent to BADL	31,8 (26,2-37,8)	3,89 (2,9-5,0)	P <0,001
Dependent to IADL	12,7 (10,6-15,0)	1,46 (0,6-2,7)	P <0,001
GDS >4	21,3 (16,6-26,6)	5,7 (4,4-7,2)	P <0,001
Cognitive impairment	17,2 (13,4-21,6)	4,2 (3,1-5,6)	p<0,001

Note: NS = not significant; COPD = chronic obstructive pulmonary disease; BADL : basic acitivities of daily living; IADL = instrumental activities of daily living; GDS = geriatric depression scale.

In conclusion, the TSHA shows a high prevalence of frailty in the population aged 65 years and older in Spain, which is very similar to that reported in other Mediterranean countries. Frailty has a big impact on health because of its strong association with cardiovascular disease, cognitive impairment, depression and disability.

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