

ARTÍCULO ORIGINAL

Profile in frail older people over 60 years of age in five Colombian cities, 2021

Fecha de recepción:

19 de junio de 2024.

Fecha de aprobación:

8 de octubre de 2024.

Forma de citar este artículo:

Arboleda VH, Muñoz DI, Cardona DS, Segura AM, Robledo CA, Segura DA, Gallo EA, Mejía SB. Perfil de fragilidad en personas mayores, de cinco ciudades de Colombia, 2021. Med UPB. 2025;44(1): 21-30. DOI:10.18566/medupb.v44n1.a03

Perfil de fragilidad en personas mayores, de cinco ciudades de Colombia, 2021 / Perfil de fragilidade em idosos, de cinco cidades da Colômbia, 2021

Víctor H. Arboleda^{1,2}, Diana Isabel Muñoz-Rodríguez³, Alejandra Segura⁴, Angela Segura Cardona⁵, Carlos Arturo Robledo Marín^{6,7}, Doris Cardona⁸, Erika Alejandra Giraldo Gallo⁹, Sebastian Bedoya Mejia¹⁰.

ABSTRACT

Objective: To establish the frailty profile of older people living in the urban areas of Bucaramanga, Medellín, Pereira, Popayán and Santa Marta in Colombia, as frail people aged 60 or over are increasingly important in primary care due to demographic change.

Methods: Cross-sectional study of 2506 participants, selected through two-stage probabilistic sampling, and classified according to the FRAIL scale, to measure frailty. A multiple correspondence model was built to define the frailty-pre-frailty and non-frailty profiles.

Results: The prevalence of people with frailty is 9.6%, and pre-frailty is 60.8%. These conditions were independently associated with female sex, depression, dependence for basic daily activities and falls. Similarly, the profile of pre-frail and frail elderly is determined by disability, falls, high nutritional risk, physical inactivity, being a woman and low socioeconomic status.

Conclusion: Frail and pre-frail elderly people have modifiable characteristics (disability, falls, nutritional risk, physical inactivity and socioeconomic status), in order to reduce the prevalence of this condition. It is recommended that elderly people be able to enter care programs at different levels, in order to contribute to healthy aging processes.

Keywords: frailty; functionality; depression; falls; elderly person.

RESUMEN

Objetivo: establecer el perfil de fragilidad de las personas mayores, residentes en la zona urbana de Bucaramanga, Medellín, Pereira, Popayán y Santa Marta en Colombia, en tanto que las personas de 60 o más años frágiles son cada vez más importantes en la atención primaria, debido al cambio demográfico.

Métodos: estudio transversal de 2506 participantes, seleccionadas a través de muestreo bietápico y probabilístico, y clasificados según la escala FRAIL, para medir la fragilidad. Se construyó un modelo de correspondencias múltiples, para definir los perfiles de fragilidad-prefragilidad y no fragilidad.

Resultados: la prevalencia de personas con fragilidad es del 9,6%, y prefragilidad del 60,8%. Estas condiciones se asociaron de manera independiente con el sexo femenino, la depresión, la dependencia para las actividades básicas cotidianas y las caídas. Igualmente, el perfil de los prefrágiles y frágiles está dado por la discapacidad, las caídas, el alto riesgo nutricional, la inactividad física, ser mujer y el estrato socioeconómico bajo.

Conclusión: las personas mayores frágiles y prefrágiles tienen características modificables (discapacidad, caídas, riesgo nutricional, inactividad física y estrato socioeconómico), a fin de reducir la prevalencia de esta condición. Se recomienda que las personas mayores puedan ingresar a programas de atención en diferentes niveles, con el fin de contribuir a los procesos de envejecimiento saludable.

Palabras clave: fragilidad; funcionalidad; depresión; accidente por caídas; persona mayor.

1. Grupo de Investigación Movimiento y Salud; Epidemiología y Bioestadística, Universidad CES. Medellín, Colombia.
2. Corazón y Aorta. Popayán, Colombia.
3. Grupo de Investigación Movimiento y Salud, Facultad de Fisioterapia, Universidad CES. Medellín, Colombia.
4. Grupo Observatorio de la Salud Pública, Universidad CES. Medellín, Colombia.
5. Grupo de Investigación Epidemiología y Bioestadística, Universidad CES. Medellín, Colombia.
6. Universidad CES. Medellín, Colombia.
7. Fundación Opción Colombia (FUNDACOL). Medellín, Colombia.
8. Grupo de Investigación Psicología, Salud y Sociedad, Universidad CES. Medellín, Colombia.
9. Doctorado en Epidemiología y Bioestadística, Universidad CES. Medellín, Colombia.
10. Proyecto SABAM, Universidad CES. Medellín, Colombia.

RESUMO

Objetivo: estabelecer o perfil de fragilidade dos idosos residentes na área urbana de Bucaramanga, Medellín, Pereira, Popayán e Santa Marta na Colômbia, enquanto as pessoas frágeis com 60 anos ou mais são cada vez mais importantes na atenção primária, devido às mudanças demográficas.

Métodos: estudo transversal com 2.506 participantes, selecionados por meio de amostragem probabilística e em dois estágios, e classificados segundo a escala FRAIL, para mensuração de fragilidade. Foi construído um modelo de correspondência múltipla para definir os perfis fragilidade- pré-fragilidade e não fragilidade.

Resultados: a prevalência de pessoas com fragilidade é de 9.6% e a pré-fragilidade é de 60,8%. Essas condições foram independentemente associadas ao sexo feminino, à depressão, à dependência para atividades básicas da vida diária e às quedas. Da mesma forma, o perfil dos pré-frágeis e frágeis é dado por deficiência, quedas, alto risco nutricional, sedentarismo, ser mulher e baixo nível socioeconômico.

Conclusão: idosos frágeis e pré-frágeis apresentam características modificáveis (incapacidade, quedas, risco nutricional, sedentarismo e nível socioeconômico), a fim de reduzir a prevalência desta condição. Recomenda-se que os idosos possam ingressar em programas de cuidados em diferentes níveis, a fim de contribuir para processos de envelhecimento saudável.

Palavras-chave: fragilidade; funcionalidade; depressão; acidente por quedas; pessoa idosa

Dirección de correspondencia:
 Víctor Hugo Arboleda
 Campo. Correo electrónico:
 arboleda.victor@uces.edu.co

INTRODUCTION

The demographic change in the world predicts the population ≥ 60 years of age will increase from 12% to 22% by 2050¹. In Colombia, an increase of this age group is also expected, according to the projections of the National Administrative Statistics Department (DANE)². By 2030, people ≥ 60 are expected to account for 17.5% of the population³. A 10% growth at the community level is estimated. Older people show heterogeneous characteristics⁴; physiological changes may result in greater risk, functional loss, and multimorbidity⁵, which may lead to a fragile state⁶.

Frailty (defined as a state of greater stress vulnerability)⁷ presents with different conceptual definitions and diagnostic tools, which hinders its standardization because of time, use of equipment and training for its screening. The Fried physical phenotype criteria and the Rockwood index for estimating frailty degree are among the most used tools⁸. Consequently, simplified detection instruments such as the FRAIL scale (fatigue, resistance, ambulation, illness, loss of weight) to help stratify people with frailty⁷ are required⁹. Despite there is no consensus regarding frailty definition and measurement¹⁰⁻¹², considering several factors and approaches of the frailty states in elderly people is required since not all of them age in neither the same context nor health condition. Consequently, their understanding, approach and conceptualization might be limited. This tool combines elements from both approaches, through which it is

intended to rapidly solve screening needs, requiring no instruments nor trained personnel for its application, *i.e.*, it may be individually completed^{9,13}.

As a result of the fast growth of the elderly population, the number of geriatricians is currently insufficient in several countries. Consequently, elderly people are being referred to other medical professionals such as hospital doctors, internal medicine specialists, and family physicians¹⁴. The situation in Colombia is similar. According to a reported research, only 5% of what is required for proper attention of the elderly population is available¹⁵. Furthermore, the prevalence of frailty in this study group in the community ranged between 4% and 59%¹⁰. In South America, approximately one in two older people is pre-frail and one in five is frail. These figures are higher than data reported in Europe and Asia¹¹. According to the National Study of Health, Well-being and Aging (SABE), a prevalence of 17.9% was established in 2015 in Colombia¹². These differences in the prevalence of the condition may be related to the various forms of measurement and approaches.

The risk of mortality is significantly increased in frail older people due to the presence of cardiovascular and respiratory diseases, cancer¹³, functional impairment associated with age¹⁴, changes in nutritional status¹⁵, lifestyle, emotional state (depression), falls¹⁶, social conditions¹⁷, and polypharmacy, all of which lead to adverse health outcomes^{12,18-23}. Therefore, the need of this population for health care services is increased by the frail condition. Updated policies and programs are

required in order to respond to current and future health needs of older people. Additionally, there is little research focused specifically on the phenotype of Rockwood deficits for frailty in the Colombian population, although the SABE study carried out this exploration with another instrument focused on the physical. Overall, there is a lack of detailed understanding of the profile of frailty in older people at the community level. In addition, few investigations have specifically addressed the Rockwood deficits phenotype regarding frailty in Colombian population. In SABE, this exploration was undertaken using a tool centered in physical activity. A thorough knowledge of elderly people frailty profile at the community level is lacking. This study aims to provide evidence in the urban community context and seeks to establish the frailty profile in people aged 60 and over, belonging to five cities in Colombia in 2021.

METHODOLOGY

Study design

Empirical, analytical, observational, cross-sectional study, of a quantitative methodology, from a primary source²⁴.

Context

Data were collected during April and May 2021 by a team of standardized interviewers within the Health and Mental Wellbeing of the Elderly 2020 (SABAM) project framework²⁵.

Participants

Participants selection

Elderly people (≥ 60 years of age), living in five urban areas in Colombia (Bucaramanga, Medellín, Pereira, Popayan, Santa Marta), where a proportion of this population exceeding the national average had been previously identified¹⁸. Those who agreed to participate signed an informed consent. Elderly subjects with cognitive impairment (Mini-Mental State Examination [MMSE] score <13)¹⁹ were excluded, as well as those under the influence of psychoactive substances.

Data collection

The information was collected using an authors' designed survey, which was applied by the interviewers following pilot testing.

INSTRUMENTS AND PROCEDURES

Frailty was measured using the scale proposed by the International Association of Nutrition and Aging (FRAIL). The scale scores range from 0 (non-frail), 1-2 (pre-frail), and higher than 2 (frail)^{9,26,27}. Several sociodemographic variables (city, age, sex, marital status, educational level, illnesses number, medications taken, socioeconomic stratum [SES] of the home, General Health Social Security System [SGSSS]) were considered. Nutritional status was measured by means of the Determine questionnaire²⁸ and sleep quality by means of the Pittsburgh Index²⁹. Health status (poor, fair, good, very good, excellent)³⁰ was self-reported. For screening of depression symptoms, the Depression scale from the Center for Epidemiological Studies Depression Scale (CESD) was used³¹. In addition, the following were used: physical activity (yes/no), falls (yes/no) for assessing functional performance, the Barthel Index for Activities of Daily Living (ADL)³², the family APGAR for family functioning³³, and the MOS scale for social performance^{33,34}.

Study design

Empirical-analytical study with quantitative methodology, An analytical cross-sectional observational study was carried out, from primary source²⁷. Information was collected between April and May 2021, through a team of standardized interviewers within the framework of the SABAM 2020 project²⁸.

Data collection

A survey designed by the authors was used to collect the information, which was pilot tested, and which was finally applied by the interviewers. The study design was probabilistic, carried out in two stages. In the first, 51 neighborhoods per city were selected as a secondary unit of the sample, through systematic random sampling; and within each neighborhood, two blocks were selected as the primary unit of the sample, by simple random sampling²⁸.

Sample size

To calculate the sample size, the Fleiss formula for finite populations was used, considering a confidence level of 95%, a sampling error of 5%, and an expected proportion of 17.9% of elderly people with frailty according to SABE Colombia. 12 and a design effect (deff) of 1.0. A 15% was added to this calculation to

correct possible loss of information. There were 2,506 elderly subjects available for analysis²⁹⁻³⁴.

Data analysis

The Jamovi statistical program version 2.3.21 was used for data analysis. To describe the participants, frequencies and percentages of categorical variables were estimated. Chi-square tests examined the relationship between frailty categories and independent variables. Likewise, raw prevalence ratios (PR) and their respective confidence intervals (CI) were calculated. Finally, an interdependence model was built. Variables showing a significant association with frailty as per the Hosmer-Lemeshow criterion ($p < 0.25$)³⁵ and no collinearity, as well as significant variables ($p < 0.05$), and biologically plausible variables were all included. Using the multiple correspondence analysis (MCA), it was assured that all the variables were categorical and relevant as per biological plausibility. In addition, all of the categories had remarks, no entered variables data were omitted and the independence of every variable was verified in order to avoid collinearity. The correspondence map was used for visualizing the associations.

Ethical considerations

The study was derived from the SABAM 2020 research²⁸, approved by the Institutional Human Research Ethics Committee of the CES University with minimal risk, resolution 8430 issued on May 23, 2019.

RESULTS

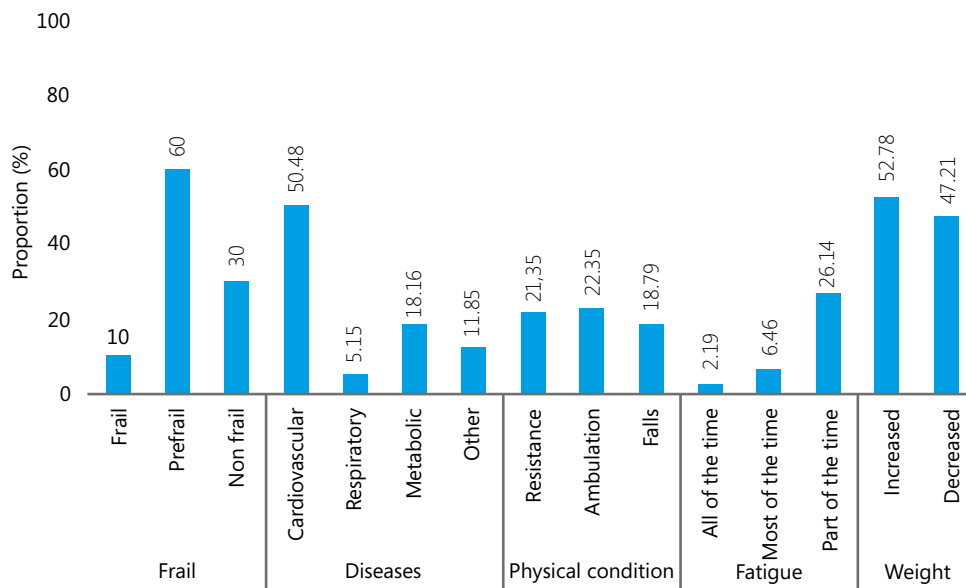
Representing approximately 20% of the total population, 2506 older people living in five cities in Colombia (Bucaramanga, Medellín, Pereira, Popayan and Santa Marta) were included in the study. The prevalence of frailty and pre-frailty reached 10% and 60%, respectively, *i.e.*, 70% had some degree of frailty. Remaining proportion were robust. It must be mentioned that main diseases are required for this construct. Cardiovascular diseases were shown to predominate (one in every two people was affected) followed by metabolic diseases (one in four people). Regarding physical condition, it was shown that the behavior ranged from walking (22.4%), resistance (21.4%), falls (18.8) and fatigue by part of the time (26.1%). In addition, five out of ten subjects had gained weight (Figure 1).

Specific frailty analysis in older people in the five cities showed statistically significant differences with $p < 0.05$ in several aspects. Significant differences were found regarding marital status, household stratum, affiliation to Social Security, number of diseases, disabilities, family functionality, depressive symptoms, ADL, falls, physical activity, nutritional status, and sleep quality.

About the number of diseases, it was found that as such number increased, the probability of being frail increased approximately by 31%. This indicates that the presence of multiple diseases in an older person is associated with a higher frailty risk.

The presence of depressive symptoms also influenced frailty. It was found that when an older person underwent

Figure 1. Characteristics of older people in five cities of Colombia (%).



depression, the probability of being frail increased by 8%. This highlights the importance of addressing mental health care in older people and its association with frailty.

In relation to ADL, it was seen that frailty was increased by 24% in subjects having experienced falls compared to those who were not frail. This highlights the importance of preventing falls and promoting safety in elderly people's environment.

Physical inactivity was also associated with frailty in older people. Frailty was increased by 27% in those with a sedentary lifestyle. Likewise, it was increased by 46%

in those depending on other people to carry out daily activities. These findings underline the importance of promoting physical activity and independence in older people in order to prevent frailty.

Finally, sleep quality also played a significant role in frailty. When it was poor, frailty was increased by approximately 15%. This highlights the importance of promoting good sleep habits and addressing sleep problems in older people as part of a comprehensive approach for frailty prevention, Table 1.

Table 1. Health conditions associated with frailty in older people. Colombia, 2021.

Characteristics	Total n (%)	Frailty		X ²	p	Prevalence ratio (95 % CI)
		Frail/Pre-frail	Robust			
		1763 (69.4%)	743 (29.6)			
City				5.13	0.274	
Bucaramanga	500 (20.0)	339 (19.2)	161(21.7)			1
Medellín	500 (20.0)	361 (20.5)	139 (18.7)			1.06 (0.98 - 1.15)
Pereira	505 (20.2)	367 (20.8)	138 (18.6)			1.07 (0.98 - 1.16)
Popayán	501(20.0)	356 (20.2)	145 (19.5)			1.04 (0.96 - 1.13)
Santa Marta	500 (20.0)	340 (19.3)	160 (21.5)			1.00 (0.92 - 1.09)
Gender				0.076	0.782	
Male	1153 (46.0)	808 (45.8)	345 (46.9)			1
Female	1353 (54.0)	955 (54.2)	398 (53.6)			1.00(0.92-1.11)
Age				2.59	0.458	
Young (60-74)	1913 (76.3)	1345 (76.3)	568 (76.4)			1
Old (75-89)	559 (22.3)	559 (22.3)	169 (22.7)			0.99 (0.88-1.11)
Oldest old (90-99)	33 (1.35)	33 (1.3)	6 (0.8)			1.16 (0.79-1.70)
Centenarians (>100)	1 (0.0)	1 (0.0)	0 (0.0)			1.42 (0.20-10.10)
Marital status				10.2	0.017	
Single	603 (24.1)	399 (22.6)	204 (27.5)			1
Married-Common law marriage	1065 (42.5)	776 (44.0)	289 (38.9)			1.10 (0.98-1.24)
Separated-Divorced	312 (12.5)	210(11.9)	102 (13.7)			1.02 (0.86-1.20)
Widowed	526 (21.0)	378(21.4)	148 (19.9)			1.09 (0.94-1.25)
Educational level				9.09	0.059	
Primary school	1309 (52.2)	943 (53.5)	366 (49.3)			0.98 (0.77-1.25)
High school	690 (27.5)	470 (26.7)	220 (29.6)			0.93 (0.72-1.19)
Technical or higher degree	202 (8.1)	128 (7.3)	74 (10.0)			0.86 (0.64-1.15)
Postgraduate	95 (3.8)	70 (4.0)	25 (3.4)			1
None	210 (8.4)	152 (8.6)	58 (7.8)			0.982 (0.74-1.30)
Household stratum				17.0	0.001	
Middle – upper (3-4)	973 (38.8)	656 (37.2)	317 (42.7)			1
Low (1-2)	1533 (61.2)	1107 (62.8)	426 (57.3)			1.07 (1.01-1.13)

Characteristics	Frailty			X ²	p	Prevalence ratio (95 % CI)
	Total n (%)	Frail/Pre-frail	Robust			
		1763 (69.4%)	743 (29.6)			
Social Security affiliation				8.72	0.003	
Yes	2441 (97.4)	1728 (98.0)	713 (96.0)			1
No	65 (2.6)	35 (2.0)	30 (4.0)			0.49 (0.30-0.79)
Number of diseases (*)				14.3	0.003	
None	1302 (52.0)	878 (49.8)	424 (57.1)			1
1	575 (22.9)	419 (23.8)	156 (21.0)			1.08 (1.01-1.15)
2	506 (20.2)	367 (20.8)	139 (18.7)			1.07 (1.1 – 1.14)
≥ 3	123 (4.9)	99 (5.6)	24 (3.2)			1.19 (1.08-1.31)
Number of medications				2.66	0.265	
None	888 (35.4)	612 (34.7)	276 (37.1)			1
1-2	1287 (51.3)	924 (52.4)	363 (48.9)			1.04 (0.94-1.15)
≥ 3	331 (13.2)	227 (12.9)	104 (14.0)			0.99 (0.85-1.16)
Health condition				2.16	0.707	
Poor	54 (2.2)	54 (2.2)	16 (2.2)			1.00 (0.71-1.42)
Fair	724 (28.9)	524 (29.7)	200 (26.9)			1.03 (0.87-1.22)
Good	1025 (40.9)	709 (40.2)	316 (42.5)			0.98 (0.84-1.16)
Outstanding	432 (17.2)	302 (17.1)	130 (17.5)			0.99 (0.83-1.20)
Excellent	271 (10.8)	190 (10.8)	81 (10.9)			1
Disability				6.31	0.012	
No	1697 (67.7)	1167 (66.2)	530 (71.3)			1
Yes	809 (32.2)	596 (33.8)	213 (28.7)			1.07 (1.01-1.28)
Social support				2.55	0.110	
Poor support	431 (17.2)	317 (18.0)	114 (15.3)			1.05 (0.93-1.19)
Proper support	2075 (82.8)	1446 (82.0)	629 (84.7)			1
Family function (APGAR)			12.3	0.006		
Functional	1910 (76.2)	1330 (75.4)	580 (78.1)			1
Slight dysfunction	383 (15.3)	285 (16.2)	98 (13.2)			1.07 (0.95-1.21)
Moderate dysfunction	101 (4.0)	80 (4.5)	21 (2.8)			1.14 (0.91-1.42)
Severe dysfunction	112 (4.5)	68 (3.9)	44 (5.9)			0.87 (0.68-1.11)
Depression symptoms				8.34	0.004	
No depression	1258 (50.2)	852 (48.3)	406 (54.6)			1
Depression	1248 (49.8)	911(51.7)	337 (45.4)			1.08 (1.02 -1.13)
Basic DLA		12.3	<.001			
Independent	1730 (69.0)	1180 (66.9)	550 (74.0)			
Dependent	776 (31.0)	583 (33.1)	193 (26.0)			1.27 (1.10 – 1.46)
Falls				47.6	<.001	
No	2035 (81.2)	1370 (77.7)	665 (89.5)			1
Yes	471 (18.8)	393 (22.3)	78 (10.5)			1.24 (1.11-1.39)
Physical activity				16.0	<.001	
Active	68 (2.7)	33 (1.9)	35 (4.7)			1
Inactive	2438 (97.3)	1730 (98.1)	708 (95.3)			1.46 (1.04-2.06)

Frailty						
Characteristics	Total n (%)	Frail/Pre-frail	Robust	X ²	p	Prevalence ratio (95 % CI)
		1763 (69.4%)	743 (29.6)			
Nutritional status				8.84	0.012	
Good	1001 (39.9)	671 (38.1)	330 (44.4)			1
Moderate risk	755 (30.1)	546 (31.0)	209 (28.1)			1.08 (0.96-1.21)
High risk	750 (29.9)	546 (31.0)	204 (27.5)			1.09 (0.97-1.22)
Sleep quality				7.2	0.007	
Good	2023 (80.7)	1399 (79.4)	624 (84.0)			1
Poor	483 (19.3)	364 (20.6)	119 (16.0)			1.09 (1.02-1.15)

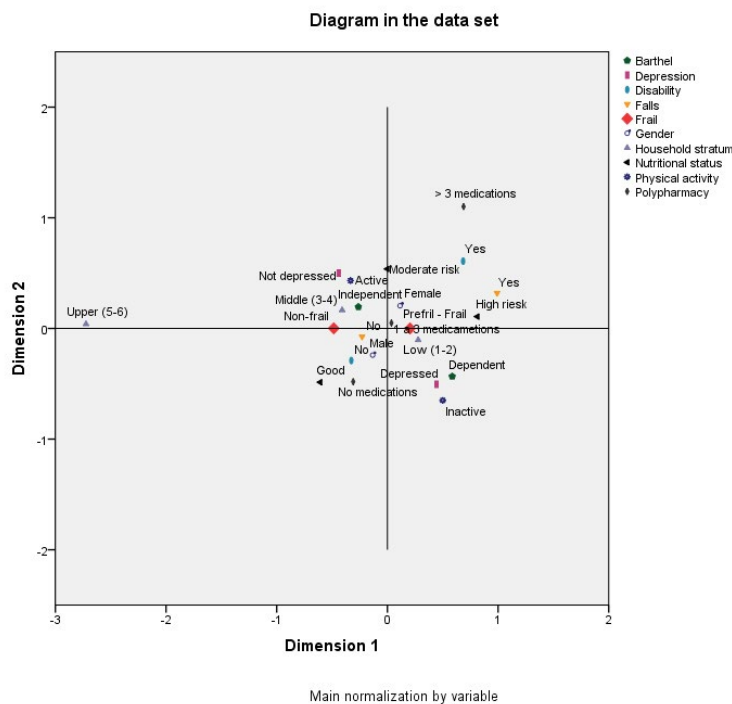
*As this variable presented collinearity with frailty, it was not entered into the final model. DLA: daily living activities.

Frailty Profile of Older People

Frail and pre-frail older people have modifiable characteristics (disability, falls, nutritional risk, physical inactivity and socioeconomic status), based on the frailty profile of the study participants, a first profile was found: It corresponded to pre-frail and frail older females of low socioeconomic condition, physically inactive, disabled, having undergone falls, and at high nutritional risk. This was associated with factors causing alterations with increased risk of adverse health outcomes, leading to old age frailty. Those who were not frail were males

from upper and middle economic level, not depressed, and on a good nutritional condition. In summary, the analysis of frailty in older people in these five cities showed statistically significant differences in several factors. The presence of multiple illnesses, depression symptoms, falls, physical inactivity, dependency, and poor sleep quality were associated with an increased risk of frailty. These findings highlight the importance of implementing interventions aimed at addressing such risk factors and promoting health and well-being in older people, Figure 2.

Figure 2. Frailty profile in older people from five cities in Colombia, 2021.



DISCUSSION

Frail and prefrail elderly people show modifiable characteristics (disability, falls, nutritional risk, physical inactivity and socioeconomic stratum). The objective of this study was to establish the profile of frailty in older people in five Colombian cities, using the FRAIL scale. Factors associated with the frail condition such as gender, basic DLA, depression, and falls were identified. Prevalence of frailty was similar to that reported in the literature³⁰, Latin America and the Caribbean¹². In 2020, the prevalence of frailty was shown to increase with age regardless of the assessment instrument used¹⁰. This may have resulted from changes in measurements because of the many instruments and approaches used, lack of a definition and of standardization for estimations in order to compare populations. However, it is important to take into account the number of pre-frail people because subjects ≥ 60 years will likely be frail within a short time, which may lead to adverse outcomes such as functional impairment, mortality, hospitalization, institutionalization, increased care needs, and risk of disability, dependence and death^{36,37}.

Same as other investigations that have shown recurrence among frail older people, an association of frail/pre-frail condition with falls was seen in this study being such what may initiate disability¹⁶. This could be explained by the aging process that leads to changes in different structures associated with physical, psychological, and social aspects thus decreasing the quality of life.

Similarly to another study³², significance with basic DLA was evident; this might be explained by the onset of early old age, with 30-40% muscle mass loss causing musculoskeletal weakness and muscle atrophy, and inducing fatigue³³.

On the other hand, according to the analysis by gender, more females were affected by frailty, similar to another study results³⁴ and SABE findings in Colombia (12). This may be due to the fact that elderly females have a longer life expectancy. In addition, they lack schooling, have lived their childhood in conditions of poverty, perform domestic tasks, have a restricted social life, and are economically dependent³⁵. All of these lead to a physiological condition of greater vulnerability to the stress factors leading to a frail condition.

Another issue are the diseases significantly associated in the study, for a higher frequency of comorbidities increases the risk of frailty. This is consistent with what has been published in the literature³⁶. Similarly to what occurs in Latin America¹², cardiovascular diseases¹⁴ and physical impairment³⁷ are related to the fragile state; these elements are clinical manifestations of two

different processes related to aging, in which functional reserve is decreased and pathological processes add up, impairing the quality of life and the functional status, and implying a poor prognosis³⁸. Our research has shown an association between frailty and disability, which is consistent with previous results of this aspect impairing the ADL in the study population³⁹. In addition, as about nutritional status, an association between higher risk and increase in frailty/pre-frailty was found, as long-term malnutrition and both insufficient protein and energy intake may lead to weight loss (one of the five criteria of the frailty phenotype), similarly to another report¹⁵. In fact, regarding depression, a significantly higher risk of frailty was identified in males than in females⁴⁰ affecting basic DLA and functionality, and involving a risk for falls¹⁶.

The main limitation of this study was its cross-sectional design, which prevented establishing causal associations. In addition, the different frailty phenotypes and measuring tools made comparing the study population outcomes difficult. Strategies were considered for having elder subjects respond the questionnaire such as allowing them a rest period upon request and observing biosafety rules because of the pandemics (physical distancing, facemask use, and handwashing)²⁵.

Finally, this study established that female gender, being dependent, and undergoing depression and falls, increase the risk of being in a frail/pre-frail condition. Likewise, this study shows a low prevalence of frailty but a high prevalence of pre-frailty in older people, with a strong association with basic DLA and falls. For this reason, to reduce the risk of frailty and associated disturbances, undertaking intervention studies in the pre-frail population in the community is essential. Consequently, aging of the world population is contributing to an increased number of people with multiple morbidities and complex attention requirements. For this reason, it has been established that frailty is associated with several factors; it is progressive, dynamical, potentially modifiable and thus, preventable. When these complex care needs are identified, it is likely to consider the importance of undertaking frailty screening in urban elderly people and intervention in the community, aiming at deploying strategies adapted to their different attention needs according to gender in order to avoid complications, and to keep both their independence and quality of life.

ACKNOWLEDGMENTS

We thank all of the elderly people living in the five participating cities, the SABAM project for allowing the inclusion of doctorate students, the Ministry of Science in Colombia, and CES University.

FINANCING

Financing for this investigation was received within the SABAM project framework with support from the Science, Technology and Innovation Ministry of Colombia and CES University, Registry code 67945²⁸.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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