

RESEARCH ARTICLE



Association between anxiety and frailty in postmenopausal women

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ABSTRACT

Objective: To explore the association between anxiety and frailty in community-dwelling postmenopausal women.

Methods: This was a cross-sectional study in which 390 postmenopausal women (aged 60–83 years) who were attending a comprehensive care program were surveyed between January 2018 and February 2020. Each participant was administered a validated Spanish version of the Hospital Anxiety and Depression Scale (HADS) to assess their anxiety status. Those scoring 8 or higher on the anxiety subscale of the HADS were indicative of anxiety. The assessment of frailty utilized the Fried's phenotype, with a diagnosis of frailty established if the participant met at least three out of the five criteria. Factors associated with frailty were analyzed using multivariate logistic regression.

Results: The mean age of participants was 70.08 years, with an average of 12.58 ± 3.19 years since menopause. Frailty was diagnosed in 43.85% of the total series, while anxiety was present in 41.08%, rising to 69.59% in participants with frailty. Neither body mass index, years since menopause, educational level, economic status, nor smoking habit demonstrated significant associations with frailty. Upon multivariate analysis, anxiety (OR 8.56), multimorbidity (OR 2.18), and age (OR 2.73) emerged as independently associated with frailty ($p < .001$, $p = .005$, and $p < .001$, respectively).

Conclusions: Among postmenopausal women with frailty, anxiety was detected in over two thirds of cases and was independently associated with frailty. This underscores the relevance of implementing anxiety screening in comprehensive care programs for postmenopausal women, with the goal of improving frailty through anxiety diagnosis and treatment.

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Introduction

Frailty and anxiety are common health concerns among postmenopausal women, each with significant implications for overall well-being and quality of life. Frailty, characterized by decreased physiological reserve and increased vulnerability to stressors, is a syndrome associated with a broad range of adverse outcomes, including physical and cognitive disability, increased health care utilization, and early death [1]. Anxiety, on the other hand, encompasses a whole spectrum of psychological symptoms, including excessive worry, fear, and nervousness, which can significantly impair daily functioning and exacerbate physical health conditions [2]. Despite being studied independently, the interplay between frailty and anxiety in postmenopausal populations remains relatively underexplored. The issue is even more relevant because of the growing evidence supporting menopause as a facilitator of frailty.

The potential relationship between frailty and anxiety in postmenopausal women merits further research. While the pathways linking these two conditions are multifaceted and complex, emerging evidence suggests bidirectional associations. On one hand, anxiety symptoms, caused by dysregulation within circuits for fear and anxiety [3], may exacerbate frailty by inducing physiological stress responses, such as increased cortisol levels and autonomic dysregulation, which can accelerate muscle loss, bone demineralization, and immune dysfunction. Conversely, frailty-related impairments in physical function and morbidity may contribute to heightened anxiety by limiting individual's perceived control over their environment and increased fear of falls or injury [4]. Understanding the potential bidirectional relationship between frailty and anxiety is crucial for developing targeted interventions to improve the holistic well-being of postmenopausal women.

The aim of this study was to evaluate the association between anxiety and frailty in a prospective series of postmenopausal

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women attending a comprehensive care program for postmenopausal women at primary care centers coordinated by the reference university hospital.

Methods

Study design and participants

This was a cross-sectional study conducted at three primary care centers in the city of Valencia, integrated into a comprehensive care program for postmenopausal women at the reference university hospital (Hospital Clínico de Valencia, Spain). All postmenopausal women (aged 60–83 years) attending the centers between January 2018 to February 2020 were invited to participate in a program aiming at examining the potential association between frailty status and anxiety (Figure 1). Postmenopausal status was defined as amenorrhea of 1 or more years. The presence of any serious illness with a life expectancy of less than a year, or cognitive or sensory impairment severely limiting their daily activities at the discretion of the investigators, were exclusion criteria.

Data collection and definitions

The clinical-epidemiological characteristics of the participants were obtained through personal interviews and physical examinations conducted by two nurses who had undergone prior training, following a structured questionnaire. The data collected were then transferred to a computerized database.

The validated Spanish version of the Hospital Anxiety and Depression Scale (HADS) was administered to each participant to ascertain their anxiety status. The HADS was developed to identify cases of anxiety and depression in non-psychiatric settings. The tool includes four items, seven for anxiety (odd numbered items scored 3–0) and seven for depression (even numbered items scored from 0 to 3). Ratings for each item are summed to provide the corresponding total anxiety and depression subscale score. A score of 8 or more in the anxiety subscale of HADS was considered indicative of the presence of anxiety [5].

The assessment of frailty was conducted using the Fried's phenotype [6], where a diagnosis of frailty was established if at least

three out of the following five criteria were met: unintentional weight loss (more than 4.5 kg in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed (when walking 4.57 m), and low physical activity (assessed by Spanish Short Version of the Minnesota Leisure Time Physical Activity Questionnaire) [7].

Social class was categorized based on self-reported financial status, reflecting the ability to cover essential monthly expenses, savings, and discretionary spending capacity. Participants categorized themselves into three primary groups: 'low' if they struggled to fully cover basic expenses, 'medium' if they consistently met basic expenses, and 'good' if their income allowed for savings and discretionary spending. Education level was classified as 'none' (indicating no certified educational level), 'primary', 'secondary', or 'university', based on the completion and certification of each respective educational stage. Comorbidity was defined as the presence of two or more chronic conditions, such as diabetes, heart failure, chronic obstructive pulmonary disease (COPD), cancer, etc. [8]. Multimorbidity was established as the presence of two or more disorders [9].

Statistical analysis

Qualitative variables were expressed as absolute and relative (percentage) frequencies and compared with chi square test or Fisher's exact test, as appropriate. Quantitative variables were compared using Student's *t*-test or analysis of variance (ANOVA) when the distribution was normal, or Mann–Whitney *U*-test when it was not normal. Multivariate analysis was performed using logistic regression, considering an α significance level of 0.05 for all tests. SPSS v. 25 software (IBM Corp., Armonk, NY) was used for statistical analysis.

Ethical aspects

This study was approved by the Clinical Research Ethics Committee of the Hospital Clínico de Valencia (registration number 170330). Those participants who agreed to participate signed an informed consent prior to their inclusion in the study. All data collected, processed, and analyzed in this work were anonymized.

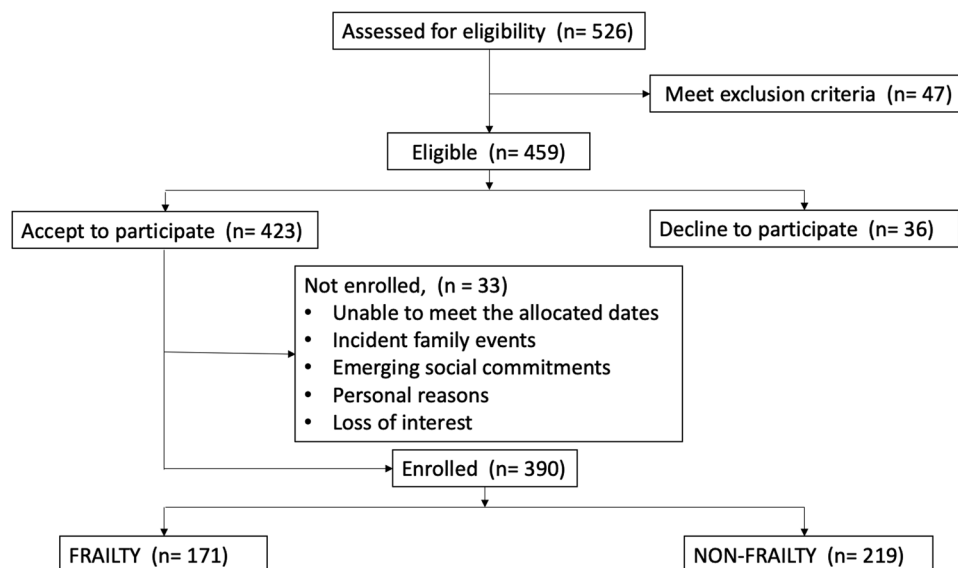


Figure 1. Flowchart of 390 postmenopausal women with and without frailty.

Results

A total of 390 postmenopausal women participated in the study, with an age of 70.08 ± 5.36 years (mean $\pm$ SD) and a range of 60–83 years. Most participants exhibited a medium to high socioeconomic status (85.13%), with only 14.87% classified as low. Primary education level was the most prevalent (45.38%), while 42.05% were categorized as having high education attainment. They were married or in a relationship in 56.92%, separated in 13.85% and single or widowed in 29.23% of cases. The average number of years since menopause was 12.58 ± 3.19 years, ranging from 6 to 24 years. The majority of women had a normal weight, with an average BMI of 27.25 ± 12.62 kg/m².

Frailty, as determined by the Fried's phenotype, was detected in 43.85% of the total series, Table 1 provides an overview of the clinical and epidemiological variables categorized by frailty status. No statistically significant differences were found between women with or without frailty regarding weight, BMI, years since menopause, marital status, educational level, socioeconomic status, or smoking status.

Anxiety, assessed by the HADS anxiety subscale with scores ranging from 0 to 21, was present in 41.08% of the total series, with a score exceeding 15 points in 7.69%. Anxiety showed a statistically significant increase in the subgroup of frail women (69.59% vs 22.37%, $p < .001$). Using multivariate logistic regression analysis, anxiety was found to be associated with frailty (OR 8.56, 95% CI 5.30–13.82, $p < .001$), as well as age (OR 2.73, 95% CI 1.63–4.51, $p < .001$), and comorbidity (OR 2.18, 95% CI 1.27–3.76, $p = .005$), as shown in Table 2.

Discussion

In this study, the systematic application of a frailty diagnostic tool, such as the Fried's Frailty Tool or Frailty Phenotype, which is the most frequently cited tool for screening frailty [10],

Table 1. Epidemiological and clinical characteristics of participants according to frailty status.

		Frailty (n=171)	Non-frailty (n=219)	p Value*
Age years	<70	48 (28.07)	101 (46.12)	<.001^b
	≥70	123 (71.93)	118 (53.88)	
Years since menopause		24.96 $\pm$ 11.63	23.77 $\pm$ 10.53	.292 ^a
Height (m)		1.59 $\pm$ 0.06	1.58 $\pm$ 0.05	.294 ^a
Weight (kg)		67.68 $\pm$ 8.97	69.90 $\pm$ 41.67	.493 ^a
Body mass index (kg/m ²)		26.68 $\pm$ 4.01	27.68 $\pm$ 16.46	.434 ^a
Waist circumference (cm)		81.84 $\pm$ 8.29	82.56 $\pm$ 9.32	.428 ^a
Marital status	Married/couple	89 (52.04)	133 (60.73)	.220 ^b
	Separated	30 (17.54)	37 (16.89)	
	Single	36 (21.06)	30 (13.70)	
	Widow	16 (9.36)	19 (8.68)	
Education level	None	17 (9.94)	32 (14.61)	.456 ^b
	Primary education	83 (48.54)	94 (42.92)	
	Secondary education	44 (25.73)	54 (24.66)	
Economic status	University	27 (15.79)	39 (17.81)	.768 ^b
	High	81 (47.38)	108 (49.31)	
	Medium	66 (38.59)	77 (35.16)	
	Low	24 (14.03)	34 (15.53)	
Multimorbidity		137 (80.12)	141 (64.38)	.001^b
Anxiety		119 (69.59)	49 (22.37)	<.001^b
Smoking habit	Ex-Smoker	32 (19.88)	48 (21.91)	.563 ^b
	Smoker	30 (27.48)	43 (19.64)	
	Non-smokers	109 (26.31)	128 (58.45)	

Data are expressed as mean $\pm$ standard deviation or frequency n (%). *p Value as determined with ^aStudent's T test or ^bthe chi-square test. Significance differences are highlighted in bold.

revealed a significant prevalence of frailty (43.85%) among postmenopausal women participating in a comprehensive health assessment program. Similarly, the global assessment of anxiety using the HADS scale revealed a high percentage of participants with anxiety. Moreover, our findings indicate a noteworthy association between anxiety and frailty, suggesting promising opportunities for frailty intervention strategies aimed at addressing anxiety.

Frailty may be conceptually defined as a clinically recognizable state in older people who have increased vulnerability, resulting from age-associated declines in physiological reserve and function across multiple organ systems, such that the ability to cope with every day or acute stressors is compromised [1]. Therefore, as anticipated, frailty showed a direct correlation with age in our postmenopausal women series, reaching 71.9% among those 70 years or older, exceeding what is typically described in the literature, with values ranging from 4% to 59% [11–14]. This fact could be attributed to the varying criteria used to define frailty and to the nature of this study, which was not conducted in the general population but rather in participants of a comprehensive care program for postmenopausal women. In this study, multimorbidity, defined by the presence of two or more chronic diseases, was independently associated with frailty regardless of age, providing an opportunity to address it through the appropriate management of these conditions. We used the list of 40 morbidities selected from a database of medical practices in UK for defining multimorbidity [9]. However, since the Fried's Physical Frailty Phenotype was used, we did not specifically assess cognitive ability, which is often associated with frailty. Additionally, significant cognitive impairment that would significantly limit activities of daily living was a reason for study exclusion. Therefore, the assessment of comorbidities was not comprehensive as it did not consider the cognitive dimension.

Outside the field of geriatrics, the assessment of patients' functional status has often been ignored. It is only recently that there has been an emerging interest in evaluating frailty among postmenopausal women [15]. During aging, there is a decline in the activity of various hormonal systems [16]. In women, one of the most significant changes is menopause, which is characterized by a transition from cyclic estradiol production to a lower and steady level of estradiol, accompanied by elevated levels of follicle-stimulating hormone [17]. However, the relationship between estrogen and frailty has been scarcely explored [15,18]. Other endocrine-metabolic, immunological and inflammatory alterations observed in menopause that could influence frailty include decreased levels of free testosterone [19], increased levels of proinflammatory cytokines (interleukin-6), acute-phase reactants, and tumor necrosis factor-alpha [20–22]. However, the mechanisms predisposing to frailty in menopausal women have not been fully elucidated to date. Further studies are necessary to get across the underlying mechanisms of this association.

While there is a clear link between frailty and depression, the association between frailty and other mental health disorders is less extensively documented. In the present study, there has been

Table 2. Factors associated with frailty in postmenopausal women: multivariate analysis by logistic regression.

Factors	OR	95% CI	p Value
Anxiety	8.56	5.30–13.82	< .001
Multimorbidity	2.18	1.27–3.76	.005
Age	2.73	1.65–4.51	< .001

Multimorbidity was established as the presence of two or more diseases. OR: odds ratio; CI: confidence interval.

a strong association between frailty and anxiety, clearly higher than that found in the few conducted studies [23–25], and much higher than that found in routine clinical practice, as anxiety is underdiagnosed in all case settings [3]. The anxiety itself can contribute to physical frailty by causing sleep disturbances, loss of appetite, increased hormonal stress, or adoption of unhealthy habits. Moreover, anxiety can lead to chronic stress with increased inflammation and other physiological changes that may contribute to frailty [26]. Conversely, frailty symptoms could lead to maladaptive psychological responses, including anxiety. However, the value of distinguishing between primary and secondary anxiety is unclear because there is growing evidence that the link between somatic illness and anxiety is bidirectional, and anxiety treatment is needed independently of both [27].

The present study is not free from limitations. Firstly, the recruitment of patients exclusively from three primary care centers with a specialized program for postmenopausal women may restrict the generalizability of the findings to broader contexts. Secondly, the specific subtype of anxiety experienced by the participants is not known, and its influence on frailty may differ among subtypes. Thirdly, the study lacks information regarding whether the diagnosis of anxiety was preexisting and if patients were undergoing treatment for it. Fourth, it is uncertain whether anxiety precedes frailty, if the relationship is reversed, or if there is a mutual influence between the two. Despite these constraints, the results underscore the significance of anxiety in postmenopausal women and its association with frailty.

Conclusion

In this study, anxiety was detected in more than half of the participants attending an integrated program for postmenopausal women, reaching over two-thirds among those women with frailty. These findings suggest an opportunity to include screening for anxiety in comprehensive care programs for postmenopausal women and open up avenues for strategies aimed at improving frailty through the diagnosis and treatment of anxiety. New studies are needed to confirm these findings and clarify the potential causal relationship between anxiety and frailty.

Authors contribution

AG-V and J F-G participated in the building of the database, the acquisition of the data, the literature search and contributed to write the manuscript. PC, A M-T and MA G-P participated in the building of the database, the acquisition of the data, the literature search, and in the critical analysis of papers' content. JJT, AA and AC participated in the conception of the manuscript, the design of the study, the literature search and the critical analysis of papers' content. AA and AGV designed the statistical analysis and completed the analysis of the data. AA y AC wrote the draft of the manuscript. All authors reviewed the manuscript critically for important intellectual content and approved the final version to be published.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All required information regarding the study protocol and the collected data will be made available upon reasonable request to researchers who provide a methodologically sound proposal. Only the analysis required to achieve the aims in the approved proposal will be permitted. Proposals should be directed to antonio.cano@uv.es.

References

- [1] The World Health Organization. Clinical consortium on healthy ageing. Topic focus: frailty and intrinsic capacity. Geneva (Switzerland): WHO; 2016. Available at: <https://apps.who.int/iris/bitstream/handle/10665/272437/WHO-FWC-ALC-17.2-eng.pdf>.
- [2] Penninx BW, Pine DS, Holmes EA, et al. Anxiety disorders. *Lancet*. 2021;397(10277):1–5. doi:10.1016/S0140-6736(21)00359-7.
- [3] Tovote P, Jonathan PF, Lüthi A. Neuronal circuits for fear and anxiety. *Nat Rev Neurosci*. 2015;16(6):317–331. doi:10.1038/nrn3945.
- [4] Tan HM, Tan PW, Wong JH, et al. Men's Health Index: a pragmatic approach to stratifying and optimizing men's health. *Korean J Urol*. 2014;55(11):710–717. doi:10.4111/kju.2014.55.11.710.
- [5] Herrero MJ, Blanch J, Peri JM, et al. A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. *Gen Hosp Psychiatry*. 2003;25(4):277–283. doi:10.1016/s0163-8343(03)00043-4.
- [6] Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146–M156. doi:10.1093/gerona/56.3.m146.
- [7] Ruiz Comellas A, Pera G, Baena Díez JM, et al. Validation of a Spanish short version of the Minnesota leisure time physical activity questionnaire (VREM). *Rev Esp Salud Publica*. 2012;86(5):495–508. doi:10.4321/S1135-57272012000500004.
- [8] Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*. 2004;59(3):255–263. doi:10.1093/gerona/59.3.m255.
- [9] Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380(9836):37–43. doi:10.1016/S0140-6736(12)60240-2.
- [10] Buta BJ, Walston JD, Godino JG, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Res Rev*. 2016;26:53–61. doi:10.1016/j.arr.2015.12.003.
- [11] Espinoza SE, Hazuda HP. Frailty in older Mexican-American and European-American adults: is there an ethnic disparity? *J Am Geriatr Soc*. 2008;56(9):1744–1749. doi:10.1111/j.1532-5415.2008.01845.x.
- [12] Santos-Eggimann B, Cuénoud P, Spagnoli J, et al. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. *J Gerontol A Biol Sci Med Sci*. 2009;64(6):675–681. doi:10.1093/gerona/glp012.
- [13] Collard RM, Boter H, Schoevers RA, et al. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc*. 2012;60(8):1487–1492. doi:10.1111/j.1532-5415.2012.04054.x.
- [14] Manfredi G, Midão L, Paúl C, et al. Prevalence of frailty status among the European elderly population: findings from the survey of health, aging and retirement in Europe. *Geriatr Gerontol Int*. 2019;19(8):723–729. doi:10.1111/ggi.13689.
- [15] Ruan H, Hu J, Zhao J, et al. Menopause and frailty: a scoping review. *Menopause*. 2020;27(10):1185–1195. doi:10.1097/GME.0000000000001612.
- [16] Lamberts SW, van den Beld AW, van der Lely AJ. The endocrinology of aging. *Science*. 1997;278(5337):419–424. doi:10.1126/science.278.5337.419.
- [17] Sipilä S, Poutamo J. Muscle performance, sex hormones and training in peri-menopausal and post-menopausal women. *Scand J Med Sci Sports*. 2003;13(1):19–25. doi:10.1034/j.1600-0838.2003.20210.x.

- [18] Carcaillon L, García-García FJ, Tresguerres JA, et al. Higher levels of endogenous estradiol are associated with frailty in postmenopausal women from the Toledo study for healthy aging. *J Clin Endocrinol Metab.* 2012;97(8):2898–2906. doi:[10.1210/jc.2012-1271](https://doi.org/10.1210/jc.2012-1271).
- [19] Cappola AR, Xue QL, Fried LP. Multiple hormonal deficiencies in anabolic hormones are found in frail older women: the women's health and aging studies. *J Gerontol A Biol Sci Med Sci.* 2009;64(2):243–248. doi:[10.1093/gerona/gln026](https://doi.org/10.1093/gerona/gln026).
- [20] Chagas EFB, Bonfim MR, Turi BC, et al. Effect of moderate-intensity exercise on inflammatory markers among postmenopausal women. *J Phys Act Health.* 2017;14(6):479–485. doi:[10.1123/jpah.2016-0319](https://doi.org/10.1123/jpah.2016-0319).
- [21] Perry CD, Alekel DL, Ritland LM, et al. Centrally located body fat is related to inflammatory markers in healthy postmenopausal women. *Menopause.* 2008;15(4 Pt 1):619–627. doi:[10.1097/gme.0b013e-318159f1a2](https://doi.org/10.1097/gme.0b013e-318159f1a2).
- [22] Vrachnis N, Zygouris D, Iliodromiti Z, et al. Probing the impact of sex steroids and menopause-related sex steroid deprivation on modulation of immune senescence. *Maturitas.* 2014;78(3):174–178. doi:[10.1016/j.maturitas.2014.04.014](https://doi.org/10.1016/j.maturitas.2014.04.014).
- [23] Bernal-López C, Potvin O, Avila-Funes JA. Frailty is associated with anxiety in community-dwelling elderly adults. *J Am Geriatr Soc.* 2012;60(12):2373–2374. doi:[10.1111/jgs.12014](https://doi.org/10.1111/jgs.12014).
- [24] Tan M, Bhanu C, Frost R. The association between frailty and anxiety: a systematic review. *Int J Geriatr Psychiatry.* 2023;38(5):e5918. doi:[10.1002/gps.5918](https://doi.org/10.1002/gps.5918).
- [25] Mutz J, Choudhury U, Zhao J, et al. Frailty in individuals with depression, bipolar disorder and anxiety disorders: longitudinal analyses of all-cause mortality. *BMC Med.* 2022;20(1):274. doi:[10.1186/s12916-022-02474-2](https://doi.org/10.1186/s12916-022-02474-2).
- [26] Sciacchitano S, Carola V, Nicolais G, et al. To be frail or not to be frail: this is the question—a critical narrative review of frailty. *J Clin Med.* 2024;13(3):721. doi:[10.3390/jcm13030721](https://doi.org/10.3390/jcm13030721).
- [27] Alonso J, Liu Z, Evans-Lacko S, et al. Treatment gap for anxiety disorders is global: results of the World Mental Health Surveys in 21 countries. *Depress Anxiety.* 2018;35(3):195–208. doi:[10.1002/da.22711](https://doi.org/10.1002/da.22711).