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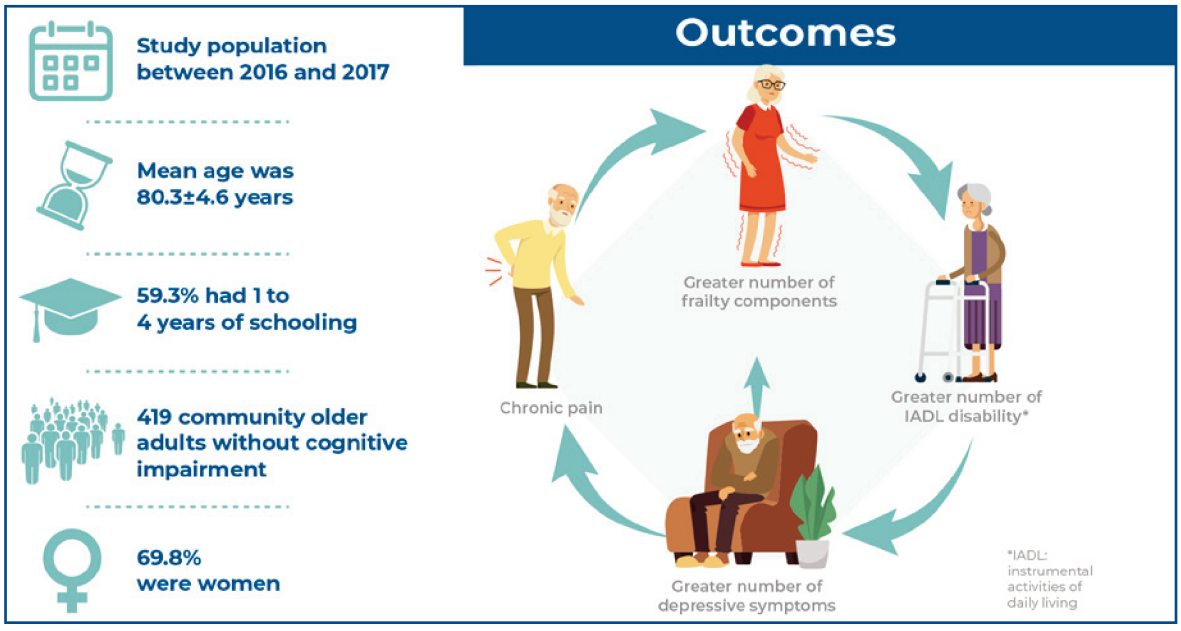
ORIGINAL ARTICLE

Relationship between chronic pain, depressive symptoms, and functional disability in community-dwelling older adults: mediating role of frailty



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In Brief

Borim et al. showed that older adults with chronic pain exhibited more depressive symptoms and frailty components. Depressive symptoms were associated with more frailty components, and those with more depressive symptoms and frailty faced greater limitations in IADL performance. Frailty appears to mediate the pathway from chronic pain to functional impairment.

Highlights

- Chronic pain is directly associated with depressive symptoms and frailty.
- Chronic pain is not directly associated with functional disability.
- Depression and frailty are both directly associated with functional disabilities.
- Frailty mediates the association between chronic pain and functional disability.

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ORIGINAL ARTICLE

Relationship between chronic pain, depressive symptoms, and functional disability in community-dwelling older adults: mediating role of frailty

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ABSTRACT

Objective: To evaluate the direct and indirect effects of chronic pain, depressive symptoms, frailty components, and functional disability through a pathway analysis approach in a sample of community-dwelling older adults. **Methods:** Data of 419 participants were cross-sectionally evaluated for the presence of depressive symptoms (Geriatric Depression Scale [15 items]), physical frailty components (phenotype criteria), chronic pain, and limitations in performing instrumental activities of daily living (functional disability scale by Lawton and Brody). Structural equation modeling via path analysis was used to explore the direct and indirect effects among these four variables. Statistical significance was set at $p<0.05$. **Results:** Of the total participants, 69.8% were women and 59.3% had low education (1-4 years); the mean age was 80.3±4.6 years. Chronic pain and depressive symptoms were directly related and were associated to frailty. The number of frailty components and depressive symptoms were directly associated with functional disability. Frailty had an indirect effect on the association between chronic pain, depressive symptoms, and functional disabilities. **Conclusion:** The pathway from chronic pain and depressive symptoms to functional disability is potentially mediated by the number of frailty components.

Keywords: Pain; Chronic disease; Depression; Disability evaluation; Frailty; Frail elderly

INTRODUCTION

Chronic pain is frequent among older adults in both higher- and lower-income countries, with a mean prevalence of 40%.[1-3] Persistent pain results in several negative outcomes and geriatric syndromes such as cognitive impairment, low physical activity levels, mobility limitations, falls, frailty, sarcopenia, poor sleep quality, low quality of life, anxiety, and depression.[4,5] Pain is also associated with a decline in ability to perform activities of daily living (ADLs) among older adults.[5-7] However, current evidence on the impact of pain on the loss of ADLs is limited to poor mobility or cognitive impairment, and other direct or indirect effects or mediators of this association have not yet been explored.[5,8] For example, depressive symptoms may mediate the association between cognitive impairment and pain.[8]

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none.

Older adults experience loss of functional performance, which may be multifactorial and include pain, frailty, and depression. Potential indirect effects may occur along the pathways of depression and frailty-two major geriatric syndromes that are bidirectionally related and strongly associated with the onset of functional disability.[9] According to a recent systematic review, pain increases the risk of developing frailty by 1.85-2 times, during an average follow-up period of 3-8 years.[10,11] Although not fully understood, according to genomic analyses, pain and frailty share several mutual underlying mechanisms, including neurological pathways.[12] A longitudinal analysis revealed that pain appears to contribute to frailty incidence through the indirect effect of depression.[13]

The simultaneous occurrence of depression and frailty in late life is frequent, especially in population-based studies. According to a recent meta-analysis, older adults with depression present a 2-3 times higher risk of developing frailty adults without depression (3-4 in 10 individuals); a similar increased odds for frailty was evident in older people with depression than in those without depression.[9] Both depression and frailty are associated with adverse health outcomes, such as falls, hospitalization, institutionalization, and death, and especially with low quality of life due to impaired ADL performance.[14-16] Their synergistic effects would increase these adverse effects; thus, there is a need to investigate the shared pathological mechanisms and risk factors, common clinical variables, and potential interactions and predictive effects of both conditions.

The mechanisms underlying the association between depression and frailty include unhealthy lifestyle and immuno-metabolic, autonomic, and endocrine dysregulation.[14,17] Although epidemiological and pathological evidence points to an intimate relationship between depression and frailty, data on clinically associated factors (*e.g.*, pain) that could explain their co-occurrence are scarce. Only few cross-sectional or longitudinal studies have explored the relationship between their co-occurrence and adverse outcomes such as functional disability.[9]

Therefore, we hypothesize that depressive symptoms and frailty have indirect and direct effects on the relationship between chronic pain and functional disabilities.

OBJECTIVE

To evaluate the direct and indirect effects of chronic pain, depressive symptoms, frailty components, and functional disability using a pathway analysis approach for a sample of community-dwelling older adults.

METHODS

Design, participants, and procedures

This cross-sectional analysis used data from the second wave of the FIBRA study (*Fragilidade em Idosos Brasileiros – Frailty in Brazilian Older Adults*) conducted between 2016 and 2017. The FIBRA study is a multicentric investigation of frailty among probabilistic samples of older Brazilians aged 65 years and above, residing in seven Brazilian cities, and selected via convenience sampling. The second wave involved participants from two sites (city of Campinas and Ermelino Matarazzo, a sub-district of the city of São Paulo).[18]

Eligibility criteria were being participants of the first wave of the FIBRA study and having a permanent residence in the city. Individuals presenting with memory problems suggestive of dementia, severe complications of stroke, severe or unstable Parkinson's disease, or visual or hearing deficits were excluded from the sample. Individuals who were bedridden, terminally ill, had cancer, or were undergoing chemotherapy treatment were also excluded.[18]

Among the 549 potential participants of the second wave of the FIBRA study, 130 were considered ineligible to answer part of the study protocol due to scoring below the cutoff score in the cognitive screening (*i.e.*, median scores in the Mini Mental State Examination [MMSE] for the respective group by years of schooling: 17 for those with 0 years of schooling, 22 for 1 to 4 years, 24 for 5 to 8 years, and 26 points for those with at least 9 years).[19] Therefore, the present analysis included information regarding 419 older adults who scored above the MMSE cutoff and provided valid responses for all questionnaire items. All participants were interviewed at home by two trained researchers.

Measures

Chronic pain was assessed through a single self-report question that investigated the presence or absence of important and persistent pain for the last six months (yes or no).

Depressive symptoms were evaluated using the Geriatric Depression Scale with 15 dichotomous questions (Geriatric Depression Scale, 15 items or GDS-15).[20] The GDS-15 is a continuous variable that ranges from 0 to 15 points. Clinically significant depressive symptoms were consistent with a GDS-15 score of >5 points.

The number of frailty components was investigated using the phenotypic criteria proposed by Fried et al.[21] Participants were classified according to the presence of each of the following five components using a continuous variable from 0 to 5:

- Unintentional weight loss in the past year (yes or no) was assessed. In case of "yes", we asked how many kilograms the participant lost, considering as affirmative only if a loss greater than 4.5kg or 5% of body weight was reported.
- Fatigue was measured using two self-report items obtained from the Center for Epidemiologic Studies Depression Scale (CES-D)[22] with four possible responses (always; most of the time; few times; never or rarely). The responses "always" or "most of the time" were considered affirmative.
- Handgrip strength was measured with a Jamar manual dynamometer (Lafayette Instruments, Lafayette, Indiana, United States) placed in the dominant hand based on three attempts, with a one-minute interval between them. Participants whose averages of the three measurements, adjusted for sex and body mass index (BMI = weight [kg] / height^2 [m]), were among the lowest 20% of the distribution were considered to have low grip strength.
- Gait speed is indicated by the average time (in seconds) spent by the participant to walk three times, in usual step, a distance of 4.6m, as recommended by Guralnik et al.[23] Participants whose average time of the three measurements was among the highest 20% for the sample were considered frail. The time averages were adjusted for median height for both men and women.
- Leisure physical activity refers to the weekly frequency and daily duration of physical exercise and sports activities performed in leisure situations based on responses to items of the Minnesota Leisure Time Activity Questionnaire.[24,25] For calculating weekly caloric expenditure in leisure activities, the number of items to which participants responded affirmatively was considered and multiplied by the number of days per week and the number of minutes per day they performed leisure physical activity. For this variable, the quintiles of the distribution for men and women were calculated separately. Participants were considered inactive if they scored in the lowest 20% of the distribution of weekly caloric expenditure (by sex).

In addition to the sum of the positive frailty components, participants were also classified as frail if three or more components were identified; as pre-frail if 1-2 components were present; and as robust when no component was observed.

The outcome variable was functional disability, which was assessed using a self-report questionnaire regarding the performance of instrumental activities of daily living (IADL). Functional disability was identified among those who reported needing partial or total assistance to perform one or more IADL based on the Lawton Instrumental Activities of Daily Living Scale.[26,27] Seven IADL were assessed, namely, calling someone by phone, using transport, shopping, cooking, performing domestic chores, using medication, and handling money. We counted the total number of IADL for which functional disability was identified.

Ethics statement

The study received approval from the Human Research Ethics Committee of the State *Universidade Estadual de Campinas*, CAAE: 49987615.3.0000.5404; # 1.332.651 and from the Human Research Ethics Committee of the *Universidade de São Paulo*, CAAE: 92684517.5.3001.5390; # 2.952.507. All participants were informed about the objectives, procedures, and ethical concerns of the study, and they signed an informed consent form in the presence of members of the research team.

Data analysis

The variables showed a non-parametric distribution. Descriptive analysis was carried out to assess the sample based on measures of absolute and relative frequency (%) for categorical variables; and mean and standard deviation for continuous variables. The percentage distributions and respective 95% confidence intervals (CIs) were estimated. A theoretical model (Figure 1) for the analysis of structural equations through path analysis was proposed to study the relationship between the variables of interest (*i.e.*, the association between chronic pain, depressive symptoms, number of frailty components, and functional disability). Structural equation analysis was performed via path analysis; this type of analysis serves as an extension of the regression model and is used to determine the relationships among a set of variables. It, therefore, enables an analysis of direct or indirect relationships between the independent and dependent variables.

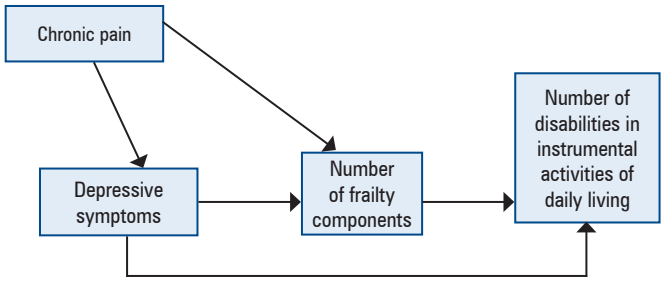

Figure 1. Hypothetical model of the relationship between the variables chronic pain, depressive symptoms, number of frailty components and number of disabilities in instrumental activities of daily living

Straight arrows indicate a direct or indirect association, whereas elliptic arrows indicate covariance. After adjusting the indicators and significance tests, the final path analysis model was constructed, which either sustains or eliminates the relationships from the previous theoretical model. The following tests and reference for significant threshold values were used in this study: χ^2 test for goodness of fit >0.05, χ^2 ratio (χ^2 / GL) <2, Standardized Root Mean Square Residual (SRMR) ≤0.10, Root Mean Square Error of Approximation (RMSEA) ≤0.08, Comparative Fit Index (CFI) ≥0.90 and Tucker-Lewis Index (TLI) ≥0.90. To analyze the goodness of fit of the proposed paths, significance tests were conducted on the path coefficients. Absolute values of t >1.96 indicate that the path has a statistically significant coefficient. Data analysis was performed using Stata software version 15.1.

RESULTS

A higher proportion of our sample of 419 participants were women (69.8%) and had 1 to 4 years of schooling (59.3%); the mean age was 80.3 years (SD±4.6). It was observed that 57.1% had chronic pain and 19.6% showed clinically significant symptoms of depression (GDS-15 >5 points). Regarding frailty status, 20.3%, 63.0%, and 16.7% were classified as robust, pre-frail, and frail, respectively. The mean number of frailty components was 1.44 (SD±1.06). At least one IADL-related disability was found in 49.6% of the sample and the total number of IADL-related disabilities ranged from 0 to 7 with a mean score of 1.32 (SD±1.79) (Table 1).

Table 1. Characteristics of the sample regarding measures of interest

Variables	%	Mean (SD)
Chronic pain (yes)	57.1	
Depressive symptoms		3.47 (±2.77)
GDS ≤5	80.4	
GDS >5	19.6	
Frailty components		1.44 (±1.06)
Level of frailty		
Robust	20.3	
Pre-frail	63.0	
Frail	16.7	
Number of IADL-related disabilities		1.32 (±1.79)
None	50.4	
≥1 disability	49.6	

IADL: Instrumental Activities of Daily Living.

After the first revision of the path analysis, acceptable values were obtained for all goodness-of-fit criteria and all path coefficients were significant ($p<0.05$). Chronic pain was removed (as a nonsignificant association) from the direct relationship with the number of IADL-related disabilities.

As shown in figure 2, several direct associations were observed between chronic pain and depressive symptoms, chronic pain and depressive symptoms in relation to the number of frailty components, and depressive symptoms and the number of frailty components in relation to the number of IADL-related disabilities. Specifically, older people who reported chronic pain had a greater number of depressive symptoms and a greater number of frailty components. Having depressive symptoms was associated with a greater number of frailty components, and those who reported a greater number of depressive symptoms and a greater number of frailty components had a greater number of IADL-related disabilities.

In addition to the direct associations, indirect associations were also observed, as shown in table 2. Chronic pain and depressive symptoms were indirectly associated with a greater number of IADL-related disabilities, an association mediated by frailty.

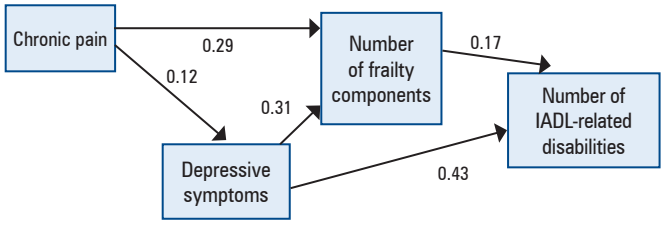

Figure 2. Final estimate of the direct effect of the hypothetical model of the relationship between the variables chronic pain, depressive symptoms, frailty components and disabilities in Instrumental Activities of Daily Living, according to the Path Analysis

Table 2. Final estimate of the indirect associations of the relationship between the variables chronic pain, depressive symptoms, frailty components and disabilities in Instrumental Activities of Daily Living, according to the Path Analysis

Indirect associations	Mediator variable	Coefficient	p value
Chronic pain → IADL-related disabilities	Frailty components	0.10	<0.001
Depression symptoms → IADL-related disabilities	Frailty components	0.05	0.034

IADL: Instrumental Activities of Daily Living.

DISCUSSION

To the best of our knowledge, this is the first study to explore both the direct and indirect relationships between chronic pain, depression, frailty, and IADL-related disability in community-dwelling older adults. Chronic pain is directly associated with depressive symptoms and frailty. These two variables were directly associated with disability. Furthermore, we explored the indirect associations between them and observed that frailty mediated the association between chronic pain, depressive symptoms, and functional disability. Finally, frailty appears to be a catalytic factor that facilitates the pathway from chronic pain to functional impairment.

Studies exploring the interactions among pain, depression, and frailty are minimal. Pathway analysis studies can potentially test hypothetical models of interactions at a lesser cost than cohort studies. In the present study, we evaluated both direct and indirect relationships between pain, depression, frailty, and functional disability, taking into account the major pathway from chronic pain to the loss of IADL-related ability. Two recent meta-analyses revealed associations between the presence of pain and frailty.[10,11] Older adults with chronic pain show an almost two-fold increase in frailty incidence.[10,11] Several mechanisms can explain the correlation between pain and frailty, including mobility problems, undernutrition, multimorbidity, depression, social isolation and loneliness, altered neurophysiology of nociception, and other neurological pathways.[12,28,29] In our study, we observed an indirect effect of depressive symptoms on the association between pain and frailty.

Depression and frailty were directly associated with IADL-related disability, with frailty mediating the association between chronic pain, number of depressive symptoms, and IADL-related disability. According to a previous study, an increase in frailty can contribute to a higher risk of functional disability with a considerable negative predictive effect in multiple organic systems.[30] The mediating effects of frailty on other disorders, syndromes, or symptoms limit IADL performance, restrict participation in community activities, and predispose individuals to injuries, hospitalization, and higher mortality.[31,32] Our study provides evidence regarding the complex interactions between pain and IADL-related disability and the potential mediating effects of depression and, especially, frailty.

Older adults suffering from chronic pain and other associated conditions, such as depressive symptoms, may have a decreased biological reserve, favoring the development of frailty and reduced functional capacity and interfering with the daily activities of people in this age group. In Brazil, population-based epidemiological surveys conducted among older adults show that chronic pain is more prevalent in women, older people with less education and in a poor economic situation, those who are insufficiently active in terms of physical activity in leisure settings,[33] and those who are dependent on others for basic ADLs and IADLs and have mobility disorders.[34]

The present study highlights the importance of a broader approach to the treatment of chronic pain, which considers multiple factors associated with the condition in the context of social inequality, as well as the need to implement multidisciplinary actions aimed at promoting healthy habits. The observed relationships can inform and guide decision-making in the care of older adults, along with setting goals and designing gerontological treatments that consider the complex network of interactions between the variables.

The strengths and limitations of this study are now addressed. Our study has several strengths, such as its design, which is based on a probabilistic community sample evaluated at home; moreover, the study excludes participants with potential cognitively impairments, employs previously recommended methods to assess the variables of interest, and involves a pathway analysis to infer mediating effects through a cross-sectional design. With regard to limitations, causality cannot be drawn from our analysis because of its cross-sectional design. In addition, several other variables, such as age, multimorbidity, and polypharmacy, can interfere in the relation between pain, depression and frailty.[32] Among these, polypharmacy is considered of utmost importance because of its association with frailty[35] and the inherent risk of geriatric syndromes and disability, especially regarding prescriptions for pain.[36] Moreover, our study had a high attrition rate (only 50% of the participants participated in the follow-up study).

CONCLUSION

In the present analyses, chronic pain was not directly associated with functional disability in community-dwelling older adults, but may indirectly contribute to functional disability through its association with frailty and depression. Longitudinal studies are recommended to replicate these findings, as they may help formulate strategies to prevent depression and frailty are relevant for older adults with chronic pain with the aim of improving long-term functional outcomes.

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AUTHORS' CONTRIBUTION

Flávia Silva Arbex Borim: conceptualization, data curation, formal analysis, methodology, writing - original draft, writing - review, and editing. Daniela de Assumpção: data curation, writing the original draft, writing the review, and editing. Mônica Sanches Yassuda: conceptualization, project administration, funding acquisition, supervision, validation, review, and editing. Henrique Trajano de Moraes Costa: investigation, review, and editing. Samila Sathler Tavares Batistoni: conceptualization, writing - original draft, writing - review, and editing. Anita Liberalesso Neri: conceptualization, project administration, funding acquisition, supervision, validation, review, and editing. Richard C. Oude Voshaar: conceptualization, methodology, writing - original draft, writing - review, and editing. Ivan Aprahamian: conceptualization, methodology, writing - original draft, writing - review, and editing.

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REFERENCES

1. Eggermont LH, Leveille SG, Shi L, Kiely DK, Shmerling RH, Jones RN, et al. Pain characteristics associated with the onset of disability in older adults: the maintenance of balance, independent living, intellect, and zest in the Elderly Boston Study. J Am Geriatr Soc. 2014;62(6):1007-16.
2. Leão Ferreira KA, Bastos TR, Andrade DC, Silva AM, Appolinario JC, Teixeira MJ, et al. Prevalence of chronic pain in a metropolitan area of a developing country: a population-based study. Arq Neuropsiquiatr. 2016;74(12):990-8.
3. Thomas E, Mottram S, Peat G, Wilkie R, Croft P. The effect of age on the onset of pain interference in a general population of older adults: prospective findings from the North Staffordshire Osteoarthritis Project (NorStOP). Pain. 2007;129(1-2):21-7.
4. Abdulla A, Adams N, Bone M, Elliott AM, Gaffin J, Jones D, Knaggs R, Martin D, Sampson L, Schofield P; British Geriatric Society. Guidance on the management of pain in older people. Age Ageing. 2013;42 Suppl 1:i1-57. Review.
5. Stubbs B, Binnekade TT, Soundy A, Schofield P, Huijnen IP, Eggermont LH. Are older adults with chronic musculoskeletal pain less active than older adults without pain? A systematic review and meta-analysis. Pain Med. 2013;14(9):1316-31. Review.
6. Lihavainen K, Sipilä S, Rantanen T, Sihvonen S, Sulkava R, Hartikainen S. Contribution of musculoskeletal pain to postural balance in community-dwelling people aged 75 years and older. J Gerontol A Biol Sci Med Sci. 2010;65(9):990-6.
7. Eggermont LH, Penninx BW, Jones RN, Leveille SG. Depressive symptoms, chronic pain, and falls in older community-dwelling adults: the MOBILIZE Boston Study. J Am Geriatr Soc. 2012;60(2):230-7.
8. van der Leeuw G, Eggermont LH, Shi L, Milberg WP, Gross AL, Hausdorff JM, et al. Pain and Cognitive Function Among Older Adults Living in the Community. J Gerontol A Biol Sci Med Sci. 2016;71(3):398-405.
9. Soysal P, Veronese N, Thompson T, Kahl KG, Fernandes BS, Prina AM, et al. Relationship between depression and frailty in older adults: a systematic review and meta-analysis. Ageing Res Rev. 2017;36:78-87. Review.
10. Saraiva MD, Suzuki GS, Lin SM, de Andrade DC, Jacob-Filho W, Suemoto CK. Persistent pain is a risk factor for frailty: a systematic review and meta-analysis from prospective longitudinal studies. Age Ageing. 2018; 47(6):785-93.
11. Lin T, Zhao Y, Xia X, Ge N, Yue J. Association between frailty and chronic pain among older adults: a systematic review and meta-analysis. Eur Geriatr Med. 2020;11(6):945-59.
12. Livshits G, Malkin I, Bowyer RC, Verdi S, Bell JT, Menni C, et al. Multi-OMICS analyses of frailty and chronic widespread musculoskeletal pain suggest involvement of shared neurological pathways. Pain. 2018;159(12):2565-72.
13. Chiou JH, Liu LK, Lee WJ, Peng LN, Chen LK. What factors mediate the inter-relationship between frailty and pain in cognitively and functionally sound older adults? A prospective longitudinal ageing cohort study in Taiwan. BMJ Open. 2018;8(2):e018716.
14. Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med. 2013;11(1):129.
15. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. Age Ageing. 2018;47(2):193-200.
16. van den Berg KS, Wiersema C, Hegeman JM, van den Brink RH, Rhebergen D, Marijnissen RM, et al. Clinical characteristics of late-life depression predicting mortality. Aging Ment Health. 2021;25(3):476-83.
17. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752-62.
18. Neri AL, Melo RC, Borim FS, Assumpção D, Cipolli GC, Yassuda MS. Avaliação de seguimento do Estudo Fibra: caracterização sociodemográfica, cognitiva e de fragilidade dos idosos em Campinas e Ermelino Matarazzo, SP. Rev Bras Geriatr Gerontol. 2022;25(5):e210224.
19. Brucki SM, Nitrin R, Caramelli P, Bertolucci PH, Okamoto IH. Sugestões para o uso do mini-exame do estado mental no Brasil. Arq Neuropsiquiatr. 2003;61(3 B):777-81.
20. Almeida OP, Almeida SA. Confiabilidade da versão Brasileira da escala de depressão em geriatria (GDS) versão reduzida. Arq Neuropsiquiatr. 1999;57(2 B):421-6.
21. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.
22. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. Psychol Aging. 1997;12(2):277-87.

23. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med. 1995;332(9):556-61.
24. Taylor HL, Jacobs DR Jr, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. J Chronic Dis. 1978;31(12):741-55.
25. Lustosa LP, Pereira DS, Dias ngela C, Britto RR, Parentoni AN, Má LS, et al. Tradução e adaptação transcultural do Minnesota Leisure Time Activities Questionnaire em idosos. Geriatr Gerontol Aging. 2011;5(2):57-65.
26. dos Santos RL, Virtuoso Júnior JS. Confiabilidade da versão brasileira da Escala de Atividades Instrumentais da Vida Diária. Rev Bras em Promoção Saúde. 2008;21(1):290-6.
27. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179-86.
28. Brown L, Young J, Clegg A, Heaven A. Pain in older people with frailty. Rev Clin Gerontol. 2015;25(3):159-71.
29. Lohman MC, Whiteman KL, Greenberg RL, Bruce ML. Incorporating Persistent Pain in Phenotypic Frailty Measurement and Prediction of Adverse Health Outcomes. J Gerontol A Biol Sci Med Sci. 2017;72(2):216-22.
30. Liu JY. The severity and associated factors of participation restriction among community-dwelling frail older people: an application of the International Classification of Functioning, Disability and Health (WHO-ICF). BMC Geriatr. 2017;17(1):43.
31. Pivetta NR, Marincolo JC, Neri AL, Aprahamian I, Yassuda MS, Borim FS. Multimorbidity, frailty and functional disability in octogenarians: A structural equation analysis of relationship. Arch Gerontol Geriatr. 2020;86:103931.
32. Schmader KE, Baron R, Haanpää ML, Mayer J, O'Connor AB, Rice AS, et al. Treatment considerations for elderly and frail patients with neuropathic pain. Mayo Clin Proc. 2010;85(3 Suppl):S26-32.
33. dos Santos FA, de Souza JB, Antes DL, d'Orsi E. Prevalence of chronic pain and its association with the sociodemographic situation and physical activity in leisure of elderly in Florianópolis, Santa Catarina: population-based study. Rev Bras Epidemiol. 2015;18(1):234-47.
34. Dellaroza MS, Pimenta CA, Duarte YA, Lebrão ML. Dor crônica em idosos residentes em São Paulo, Brasil: prevalência, características e associação com capacidade funcional e mobilidade (Estudo SABE). Cad Saude Publica. 2013;29(2):325-34.
35. Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero Á, Inzitari M, Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: a systematic review. Br J Clin Pharmacol. 2018;84(7):1432-44. Review.
36. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019;67(4):674-94.