



MedUNAB  
ISSN: 0123-7047  
ISSN: 2382-4603  
medunab@unab.edu.co  
Universidad Autónoma de Bucaramanga  
Colombia

Arauna, Diego; Navarrete, Simón; Molina, Nacim; Reyes,  
Lemuel; Rojas, Juan Pablo; Fuentes, Eduardo; Palomo, Iván  
Relation of frailty and polypharmacy on cognitive impairment in Chilean Older Adults  
MedUNAB, vol. 28, núm. 2, 2025, Agosto-Noviembre, pp. 289-300  
Universidad Autónoma de Bucaramanga  
Santander, Colombia

DOI: <https://doi.org/10.29375/01237047.5107>

Disponible en: <https://www.redalyc.org/articulo.oa?id=71983381002>

- ▶ [Cómo citar el artículo](#)
- ▶ [Número completo](#)
- ▶ [Más información del artículo](#)
- ▶ [Página de la revista en redalyc.org](#)

redalyc.org

Sistema de Información Científica Redalyc  
Red de revistas científicas de Acceso Abierto diamante  
Infraestructura abierta no comercial propiedad de la academia



## REVISTA DE LA FACULTAD DE CIENCIAS DE LA SALUD

Vol. 28(2):289-300, August - November 2025  
i-ISSN 0123-7047 e-ISSN 2382-4603



Original article

# Relation of frailty and polypharmacy on cognitive impairment in Chilean Older Adults

Relación entre la fragilidad y la polifarmacia en el deterioro cognitivo de los adultos mayores chilenos

Relação entre fragilidade e polifarmácia no declínio cognitivo de idosos chilenos

**Diego Arauna**  

[darauna@utalca.cl](mailto:darauna@utalca.cl)

Thrombosis Research Center, Medical Technology School. Department of Clinical Biochemistry and Immunohaematology, Faculty of Health Sciences, Universidad de Talca. Talca, Chile.

**Simón Navarrete**  

[snavarretep@utalca.cl](mailto:snavarretep@utalca.cl)

Thrombosis Research Center, Medical Technology School. Department of Clinical Biochemistry and Immunohaematology, Faculty of Health Sciences, Universidad de Talca. Talca, Chile.

**Nacim Molina**  

[nacim.molina@gmail.com](mailto:nacim.molina@gmail.com)

Thrombosis Research Center, Medical Technology School. Department of Clinical Biochemistry and Immunohaematology, Faculty of Health Sciences, Universidad de Talca. Talca, Chile.

**Lemuel Reyes**  

[lemuel.reyes.b@gmail.com](mailto:lemuel.reyes.b@gmail.com)

Thrombosis Research Center, Medical Technology School. Department of Clinical Biochemistry and Immunohaematology, Faculty of Health Sciences, Universidad de Talca. Talca, Chile.

**Juan Pablo Rojas**  

[jprojasburgos@gmail.com](mailto:jprojasburgos@gmail.com)

Thrombosis Research Center, Medical Technology School. Department of Clinical Biochemistry and Immunohaematology, Faculty of Health Sciences, Universidad de Talca. Talca, Chile.

**Eduardo Fuentes**  

[edfuentes@utalca.cl](mailto:edfuentes@utalca.cl)

Thrombosis Research Center, Medical Technology School. Department of Clinical Biochemistry and Immunohaematology, Faculty of Health Sciences, Universidad de Talca. Talca, Chile.

**Iván Palomo**  

[ipalomo@utalca.cl](mailto:ipalomo@utalca.cl) 

Thrombosis Research Center, Medical Technology School. Department of Clinical Biochemistry and Immunohaematology, Faculty of Health Sciences, Universidad de Talca. Talca, Chile.

### ARTICLE INFORMATION:

Article received: July 22, 2024

Article accepted: September 01, 2025

DOI: <https://doi.org/10.29375/01237047.5107>

**How to reference.** Arauna D, Navarrete S, Molina N, Reyes L, Rojas JP, Fuentes E, et al. Relation of frailty and polypharmacy on cognitive impairment in Chilean Older Adults. MedUNAB [Internet]. 2025;28(2):289-300. doi: <https://doi.org/10.29375/01237047.5107>



VIGILADA MINEDUCACIÓN

## Author Contributions

### DA, SN, NM.

Data curation and writing-original draft preparation. **DA, SN, IP.** Methodology, figures and software.

### DA, JR, LR.

Visualization and investigation. **EF and IP.** Supervision.

### IP, EF, and DA.

Validation. **DA, SN.** writing-reviewing and editing. All authors reviewed the manuscript.

## ABSTRACT

**Introduction.** The accelerated aging of the population increases the risk of the appearance of geriatric complications, such as cognitive damage. This damage has been related to frailty syndrome and polypharmacy in European cohorts, however, its relationship has not been fully clarified in Latin-American older people. This study aimed to evaluate the relationship between cognitive impairment, polypharmacy, and the frailty syndrome in Chilean older adults. **Methodology.** The investigation was designed as a cross-sectional study. The total of participants was 1,205 older adults, 65 years old and older. The presence or frailty was determined according to Fried Criteria. Polypharmacy status was evaluated employing a validated questionnaire conducted by a trained interviewer. The cognitive state was determined by the Mini-Mental State Examination. **Results.** The prevalence of cognitive impairment in the studied transversal was 19%. Older adults with cognitive impairment had a higher frailty score ( $2.39 \pm 1.45$ ,  $p < 0.001$ ), a higher prevalence of frailty, and a higher prevalence of polypharmacy (45.6%,  $p = 0.0016$ ) compared to older adults with normal cognition. The frailty criteria weight loss (OR: 1.88, CI= 1.22-2.90,  $p = 0.004$ ), exhaustion (OR: 2.66, CI= 1.89-3.76,  $p < 0.001$ ), slowness (OR: 2.10,  $p < 0.001$ ), and low physical activity (OR: 1.59,  $p = 0.009$ ) were associated with cognitive impairment, however, the weakness criteria did not present a significant association (OR: 1.29, CI=0.94-1.80,  $p = 0.119$ ). **Discussion.** Cognitive impairment was present in 19% of aged and was related to aging, lower educational level, living alone, frailty, and polypharmacy. **Conclusions.** Interventional strategies targeting frailty and excess consumption of medications may be a promising approach to prevent cognitive impairment.

### Keywords:

Frailty; Polypharmacy; Aging; Aged; Cognitive Aging; Mental Status and Dementia Tests; Cross-Sectional Studies; Geriatrics

## RESUMEN

**Introducción.** El envejecimiento acelerado de la población aumenta el riesgo de aparición de complicaciones geriátricas, como el deterioro cognitivo. Este deterioro se ha relacionado con el síndrome de fragilidad y la polifarmacia en cohortes europeas; sin embargo, su relación no se ha aclarado completamente en las personas mayores latinoamericanas. El objetivo de este estudio fue evaluar la relación entre el deterioro cognitivo, la polifarmacia y el síndrome de fragilidad en adultos mayores chilenos. **Metodología.** El estudio se diseñó como un estudio transversal. El total de participantes fue de 1205 adultos mayores, de 65 años o más. La presencia de fragilidad se determinó según los criterios de Fried. El estado de polifarmacia se evaluó mediante un cuestionario validado realizado por un entrevistador capacitado. El estado cognitivo se determinó mediante el Mini-Mental. **Resultados.** La prevalencia del deterioro cognitivo en el estudio transversal fue del 19%. Los adultos mayores con deterioro cognitivo tenían una puntuación de fragilidad más alta ( $2.39 \pm 1.45$ ,  $p < 0.001$ ), una mayor prevalencia de fragilidad y una mayor prevalencia de polifarmacia (45.6%,  $p = 0.0016$ ) en comparación con los adultos mayores con cognición normal. Los criterios de fragilidad pérdida de peso (OR: 1.88, IC = 1.22-2.90,  $p = 0.004$ ), agotamiento (OR: 2.66, IC = 1.89-3.76,  $p < 0.001$ ), lentitud (OR: 2.10,  $p < 0.001$ ) y baja actividad física (OR: 1.59,  $p = 0.009$ ) se asociaron con deterioro cognitivo; sin embargo, los criterios de debilidad no presentaron una asociación significativa (OR: 1.29, IC=0.94-1,80,  $p = 0.119$ ). **Discusión.** El deterioro cognitivo estaba presente en el 19% de las personas mayores y estaba relacionado con el envejecimiento, el bajo nivel educativo, el hecho de vivir solo, la fragilidad y la polifarmacia. **Conclusiones.** Las estrategias de intervención dirigidas a la fragilidad y al consumo excesivo de medicamentos pueden ser un enfoque prometedor para prevenir el deterioro cognitivo.

### Palabras clave:

Fragilidad; Polifarmacia; Envejecimiento; Anciano; Envejecimiento Cognitivo; Pruebas de Estado Mental y Demencia; Estudios transversales; Geriátrica

## RESUMO

**Introdução.** O envelhecimento acelerado da população aumenta o risco de complicações geriátricas, como o declínio cognitivo. Esse declínio tem sido associado à síndrome de fragilidade e à polifarmácia em grupos europeus; no entanto, sua relação ainda não foi totalmente esclarecida em idosos latino-americanos. O objetivo deste estudo foi avaliar a relação entre o declínio cognitivo, a polifarmácia e a síndrome de fragilidade em idosos chilenos. **Metodologia.** O estudo foi delineado como um estudo transversal. O total de participantes foi de 1205 idosos, com 65 anos ou mais. A presença de fragilidade foi determinada de acordo com os critérios de Fried. O estado de polifarmácia foi avaliado através de um questionário validado, realizado por um entrevistador treinado. O estado cognitivo foi determinado através do Mini-Mental. **Resultados.** A prevalência de declínio cognitivo no estudo transversal foi de 19%. Os idosos com declínio cognitivo apresentaram uma pontuação de fragilidade mais elevada ( $2.39 \pm 1.45$ ,  $p < 0.001$ ),

maior prevalência de fragilidade e maior prevalência de polifarmácia (45.6%,  $p = 0.0016$ ) em comparação com os idosos com cognição normal. Os critérios de fragilidade perda de peso (OR: 1.88, IC = 1.22-2.90,  $p = 0.004$ ), exaustão (OR: 2.66, IC = 1.89-3.76,  $p < 0.001$ ), lentidão (OR: 2.10,  $p < 0.001$ ) e baixa atividade física (OR: 1.59,  $p = 0.009$ ) foram associados ao declínio cognitivo; no entanto, os critérios de fraqueza não apresentaram associação significativa (OR: 1.29, IC=0.94-1.80,  $p = 0.119$ ). **Discussão.** O declínio cognitivo estava presente em 19% dos idosos e estava relacionado com o envelhecimento, o baixo nível de escolaridade, o fato de viver sozinho, a fragilidade e a polifarmácia. **Conclusões.** As estratégias de intervenção direcionadas à fragilidade e ao consumo excessivo de medicamentos podem ser uma abordagem promissora para prevenir o declínio cognitivo.

#### Palavras-chave:

Fragilidade; Polimedicação; Envelhecimento; Idoso; Envelhecimento Cognitivo; Testes de Estado Mental e Demência; Estudos Transversais; Geriatria

## Introduction

The percentage of people aged 60 years or older is increasing significantly worldwide. According to World Health Organization (WHO) data, in developed countries, this population comprises between 20 and 30% of the total population (1). In Chile, the population of 65 years or older is 11.9% (2). By 2050, it is estimated that there will be approximately 25% of people 65 years or older (3). The aging of the population is a relevant issue since it represents a considerable challenge for the health systems in the country and the world (4). Aging is known to be a risk factor strongly related to chronic diseases and cognitive impairment (5,6). The cognitive functions include a range of intellectual processes such as memory, language, visual and spatial processing, abstract thinking, and perception of external stimuli, critical determinants of the quality of life and health of the elderly (7-9). The deterioration process of one or several of these capacities is defined as cognitive impairment and ranges from mild cognitive impairment to dementia (10,11). In different countries in America, Europe, and Asia, the most used surveillance tool is the Mini-Mental State Examination (MMSE) (12), which is executed within preventive medicine programs for the elderly (13-15). Cognitive impairment is more prevalent in older people, observing a global prevalence of close to 19% in this age group. In contrast, in countries such as Spain and Chile, the prevalence of close to 18% and 26% are observed, respectively (16-18).

Early identification of frailty syndrome is relevant since it has been widely one of the leading causes of disability and dependence in low and middle-income countries and has currently been identified as a critical risk factor in the development of cognitive impairment and polypharmacy (18-21). Frailty predisposes individuals to a range of adverse health events, including hospitalization (1.2-1.8 times), falls and fractures (1.2-2.8 times), disability in performing activities of daily living (1.6-2.9 times), and mortality (1.8-2.3 times) (22,23). Although there

is not a consensus operational definition for frailty, the one proposed by Fried is widely used as Physical Frailty (24). Different studies suggest that frailty syndrome is associated with cognitive impairment, emerging the concept of cognitive frailty (25,26); however, more extensive studies are needed in South American cohorts due to genetic and sociodemographic differences from European cohorts (27-30). In this context of interaction between the process of cognitive damage and frailty in older people, the relevance of different mediating factors has emerged, with polypharmacy being a key point (31-33). Polypharmacy is defined as the daily consumption of 5 or more different medications and is strongly associated with a higher risk of hospitalization, mortality, and frailty (34-36). This way, was carried out the current study to evaluate the relationship of the risk factors of “cognitive impairment” and “polypharmacy” with the frailty syndrome in a representative cohort of Chilean older people.

The relevance of different mediating factors has emerged, with polypharmacy being a key point, that is strongly associated with a higher risk of frailty.

## Methodology

### Study design

A cross-sectional study design was used to assess the relation of frailty and polypharmacy on cognitive impairment in Chilean Older Adults.

### Participants

The individuals studied participated in an investigation conducted by the Interdisciplinary Excellence Research Program on Healthy Aging (PIEI-ES) (37). Briefly, this cross-sectional study was conducted between September 2016 and October 2017 in healthcare centers in the Maule Region in central Chile. The total sample was 1,205 older adults. The sample size calculation

was made considering a significance level of 0.05 (two-sided), 80% power, loss to follow-up rate of 20%, and a prevalence of frailty syndrome in Chile of approximately 22%. The inclusion criteria were an age of 65 years or more, and the exclusion criteria were the inability to walk or talk and the presence of neurodegenerative disease (dementia, Parkinson's disease, and others) or terminal illness. All participants signed informed consent. All subjects underwent a standardized evaluation that included interviews and physical examinations. This study was approved by the Scientific Ethics Committee from the University of Talca.

### ***Evaluation of Cognitive Function***

The cognitive state of the subjects was evaluated using a short version of the MMSE developed by Folstein et al. in 1975 and validated in Chile (12,38). This version is used in the annual preventive medicine examination for people 65 years and older applied in primary health care centers in Chile (39). Briefly, this questionnaire consists of 6 sections to assess: 1) temporal and spatial orientation; 2) short-term memory; 3) attention, concentration, abstraction, understanding, memory, and intelligence; 4) ability to follow instructions; 5) long-term memory, and 6) constructive visual capacity. The total positive score of this abbreviated MMSE is 19 points, a total score of 19/19 points represents the highest possible score, suggests no evidence of cognitive impairment. According to the instrument, a score  $\leq 13$  was considered altered cognition, and a score  $\geq 14$  was normal cognition. With this cut-off point, was stratified the cohort into two groups: normal cognition (score  $\geq 14$  in MMSE) and altered cognition (score  $\leq 13$  in MMSE). MMSE consists of a questionnaire that assesses orientation, attention, memory, language, and visual-spatial skills (12,40). It consists of 11 items, concentrating only on cognitive aspects such as temporal and spatial orientation, immediate and delayed recall of 3 words, attention or calculation, the nomination of 2 objects, repetition of a sentence, understanding of a verbal and a written command, writing of a sentence and a copy of a diagram (12,13).

### ***Diagnosis of Frailty Syndrome***

The diagnosis of frailty syndrome was determined by Fried et al. (24). It was based on the presence or absence of slowness, weakness, weight loss, exhaustion, and low physical activity. Briefly, slowness was defined according to a cut-off ( $< 0.8$  m/s) on three-meter walking at the usual place, adjusted for sex and height. To assess weakness, strength was measured with an Electronic Handgrip Dynamometer (Camry, City Industry, USA),

according to a sex-specific cut-off (male  $< 27$  kg, female  $< 15$  kg)(42). Unintentional weight loss was defined as self-reported loss of at least 5 kg in the previous six months. Exhaustion was classified when participants provided a positive answer to any of the following two questions from the Center for Epidemiological Studies Depression Scale: "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". Finally, low physical activity was defined by difficulty walking using two questions "Do you have difficulty walking a block?" or "Do you have difficulty climbing several flights of stairs without resting?". Subjects were classified as frail if they met three or more of these components, pre-frail if subjects met one or two components, and non-frail or robust if none of the components was present (42).

### ***Determination of Polypharmacy***

Data about polypharmacy was collected through an interview as previously described (43). A pre-trained interviewer asked the subject, "How many different drugs do you use prescribed by a doctor?". If the patient did not know his/her pharmacological treatment, a relative or caregiver responsible for the elderly person was contacted by telephone. The interviewer also asked the subject, "From the following list of drugs, which ones do you consume?". Was categorized the total amount of drugs consumed into three categories: non-polypharmacy (0–4 drugs), polypharmacy (5–9 drugs), and hyperpolypharmacy (10 or more drugs), as described by Gnjdic et al. (44).

### ***Statistical analyses***

Data obtained was analyzed using the SPSS Statistics software version 17 (SPSS Inc., Chicago, Ill., USA). Continuous variables were expressed as mean  $\pm$  SD and 95% CI, and categorical variables were expressed as percentages and a 95% confidence interval (CI). In the analysis of differences between groups, the chi-squared test was used to assess for potential differences in categorical variables, and the Student-T test or the Mann-Whitney U test, as appropriate, to evaluate for possible differences in continuous variables between subgroups. Continuous variables were grouped to create ordinal categorical (binary) variables. Logistic regression models were performed to analyze the association between frailty and the studied variables, unadjusted and adjusted for age and gender. Potential multicollinearity was evaluated in regression analysis (tolerance  $> 0.10$  and variance inflation factor  $< 4$ ). The two-tailed p-values lower than 0.05 were considered statistically significant.

## Results

As shown in Table 1, the study sample consisted of 1205 individuals with an average age of  $73 \pm 5.9$  years, where 68% were women. According to MMSE classification, the sample was divided into two groups: the normal cognitive group (67.2% women) and the impaired cognitive group (69.9% women). No difference was observed in the male/female proportion between the groups the altered cognition group was older ( $75.9 \pm 6.5$  years old) compared to the normal cognition group ( $72.7 \pm 5.6$  years old;  $p < 0.0001$ ). Also, the altered cognition group had a shorter education ( $5.9 \pm 4.0$  years) compared to the normal cognition group ( $7.5 \pm 4.4$  years;  $p < 0.0001$ ). In the altered cognition group, was

observed a higher proportion (32.3%) of patients living alone compared to the normal cognition group (23.8%;  $p = 0.0089$ ). According to the area of residence, 76.8% of older adults with normal cognition live in urban areas, while 23.2% live in rural areas. Concerning the altered cognition group, 79.9% live in the urban area and 19.1% in the rural area ( $p = 0.3352$ ). According to frailty status, considerable differences are observed. The normal cognition group presents 41.8% of non-frail people, 40.1% of pre-frail persons, and 18.1% of frail people. The altered cognition group showed a decrease in the prevalence of non-frail people (14.9%) ( $p < 0.0001$ ) and an increase in the presence of pre-frail people (33.3%) ( $p = 0.0596$ ) and frail people (51.8%) ( $p < 0.0001$ ).

**Table 1.** Characteristics of the population under study according to the cognitive state by MMSE.

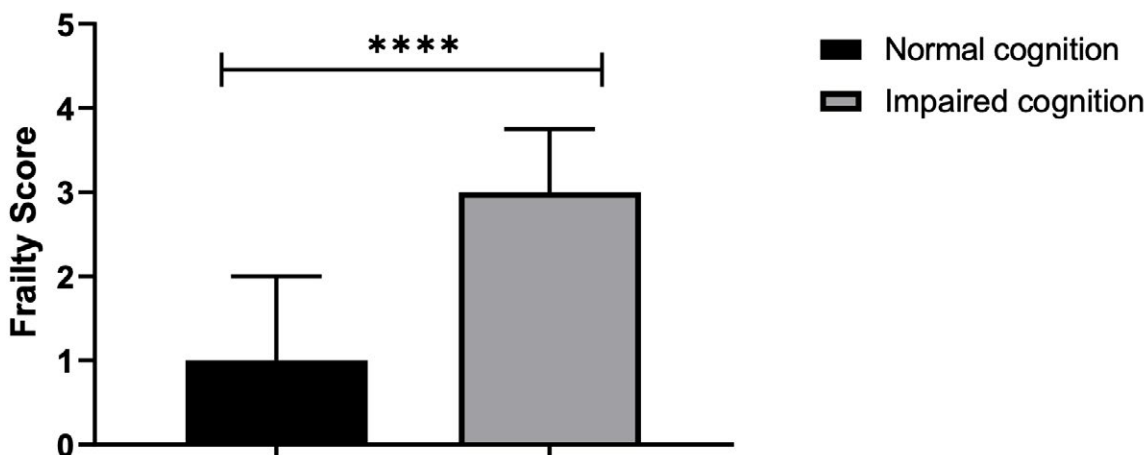
Characteristics	Total sample (n=1205)	Normal cognition (n=976)	Altered cognition (n=229)	P-value
Gender [%, 95% CI]				
Male	32 (29.7–35.0)	32.8 (29.9–35.8)	30.1 (24.6–36.4)	0.4799
Female	68 (65.0–70.4)	67.2 (64.2–70.1)	69.9 (63.6–75.4)	
Age (years) [Mean (SD)]	<b><math>73.0 \pm 5.9</math></b>	<b><math>72.7 \pm 5.6</math></b>	<b><math>75.9 \pm 6.5</math></b>	<b>&lt;0.0001</b>
Years of Education [Mean (SD)]	<b><math>7.2 \pm 4.4</math></b>	<b><math>7.5 \pm 4.4</math></b>	<b><math>5.9 \pm 4.0</math></b>	<b>&lt;0.0001</b>
Living alone, [%, 95% CI]	24 (21.8–26.8)	23.8 (21.2–26.5)	32.3 (20.9–32.3)	0.0089
Residence Area [%, 95% CI]				
Urban	77 (74.9–79.8)	76.8 (74.1–79.4)	79.9 (74.2–84.6)	0.3352
Rural	23 (20.2–25.0)	23.2 (20.6–25.9)	19.1 (15.4–25.8)	
Prevalence of Frailty [%, 95% CI]				
Non-frail	36.5 (33.8–39.3)	41.8 (38.6–44.7)	14.9 (10.9–20.1)	<b>&lt;0.0001</b>
Pre-frail	38.9 (36.2–41.7)	40.1 (37.1–43.3)	33.3 (27.5–39.7)	0.0596
Frail	24.6 (22.2–27.1)	18.1 (15.9–20.7)	51.8 (45.3–58.2)	<b>&lt;0.0001</b>
Polypharmacy status [%, 95% CI]				
Non-polypharmacy	60.4 (57.6–63.1)	62.5 (59.4–65.5)	50.9 (44.4–57.3)	0.0016
Polypharmacy	37.6 (34.9–40.4)	35.9 (32.9–38.9)	45.6 (39.3–52.1)	0.0063
Hyper-polypharmacy	2.0 (1.3–2.9)	1.6 (1.0–2.7)	3.5 (1.8–6.8)	0.1084

Fisher exact test was used to assess differences in proportions. Mann-Whitney test was used to assess differences in means. The bold text indicates a statistically significant difference between groups.

**Source:** prepared by authors

Regarding polypharmacy status, the normal cognition group presented a prevalence of 62.5% of people without polypharmacy, 35.9% of people with polypharmacy, and 1.6% of people with hyper-polypharmacy. The altered cognition group presents a decrease in the prevalence of non-polypharmacy status (50.9%) ( $p = 0.0016$ ) and an increase in the prevalence of polypharmacy status (45.6%) ( $p = 0.0063$ ) and hyper-polypharmacy status (3.5%) ( $p = 0.1084$ ).

Figure 1 shows the frailty score in older adults with and without cognitive impairment. It is observed that those elderly with cognitive impairment have a higher frailty score ( $2.39 \pm 1.45$ ) than those without cognitive impairment ( $1.18 \pm 1.26$ ) with this difference being statistically significant ( $p < 0.0001$ ). The prevalence of altered cognition increases following the increase of positivity of frailty criteria, suggesting a possible correlation.



**Figure 1.** Frailty score in older adults with and without cognitive impairment. Normal cognition group, n=976; Impaired cognition group, n=229. The statistical comparison was made by the Whitney Test. \*\*\*\*, p<0.0001. The bars represent the median and interquartile range.

Source: prepared by authors

The associations between frailty criterion and cognitive impairment through unadjusted logistic regression are shown in Table 2. When comparing the group of normal cognitive status with the group with cognitive impairment in each of the different Fried frailty criteria (24), associations with cognitive impairment are observed in the

following criterion: weight loss (OR = 2.96, CI = 1.98-4.43), exhaustion (OR = 4.46, CI = 3.30-6.24), slowness (OR = 3.74, CI = 2.77-5.04), low physical activity (OR = 3.46, CI = 2.57-4.65) and weakness (OR = 1.91, CI = 1.42-2.58).

**Table 2.** Contribution of Fried Frailty Criteria to cognitive impairment in older adults.

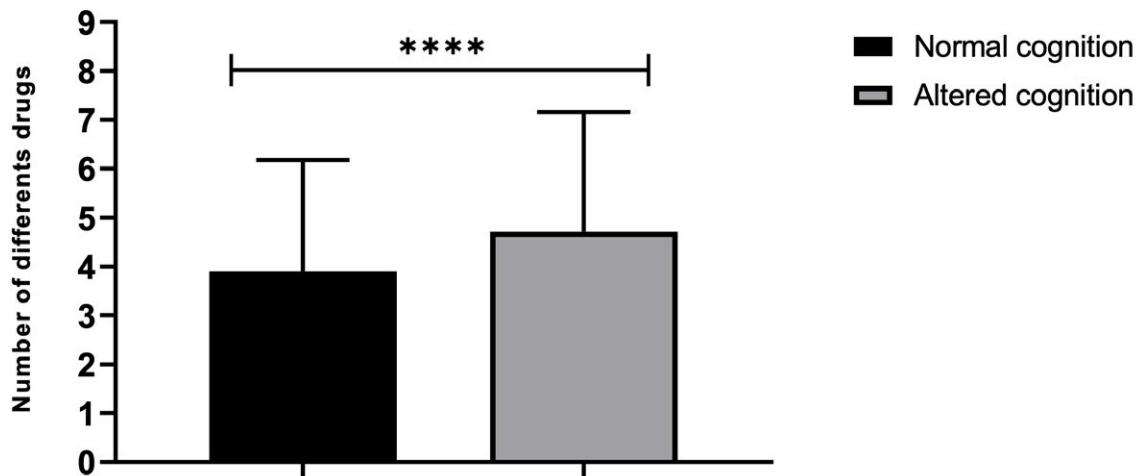
Logistic Regressions				
Not-adjusted logistic regression				
Fried Criteria	Normal Cognition vs Altered Cognition			
	OR (95% CI)			p-value
Weight loss	2.96 (1.98-4.43)			<0.0001
Exhaustion	4.46 (3.30-6.24)			<0.0001
Slowness	3.74 (2.77-5.04)			<0.0001
Low physical activity	3.46 (2.57-4.65)			<0.0001
Weakness	1.91 (1.42-2.58)			<0.0001
Multiple adjusted logistic regression				
Covariable	Tolerancia	VIF	OR (IC 95%)	
Weight loss	0.955	1.047	1.88 (1.22-2.90)*	
Exhaustion	0.746	1.340	2.66 (1.89-3.76)***	
Slowness	0.770	1.299	2.10 (1.50-2.95)***	
Low physical activity	0.712	1.405	1.59 (1.12-2.26)*	
Weakness	0.933	1.072	1.29 (0.94-1.80)	

OR: odds ratio, CI: confidence interval. VIF: variance inflation factor. \*p<0.05; \*\*\*p<0.001. Variables were selected according to their significance in the univariate model, and the model was also adjusted for sex, age, and years of education.

Source: prepared by authors

When the significant variables of the group with cognitive impairment are analyzed against the group of normal cognitive status using multivariate regression adjusted (all the criteria of fragility according to Fried were considered covariates for adjustment), the criteria weight loss (OR= 1.88, CI= 1.22-2.90), exhaustion (OR= 2.66, CI= 1.89-3.76), slowness (OR= 2.10, CI= 1.50-2.95), and low physical activity (OR= 1.59, CI= 1.12-2.26) remained associated with cognitive impairment (Table 2). In these analyses, weakness (OR= 1.29, CI= 0.94-1.80)

was no longer significantly associated with cognitive impairment. Collinearity analyses are also shown in Table 2. It is observed that none of the variables had positive indicators of the presence of collinearity (tolerance >0.10 and VIF<4). On the other hand, when cognitive status was compared with the number of drugs consumed (Figure 2), it was observed that older adults with altered cognition (4.72±2.45 daily medications) had a higher daily drug use compared to older adults with normal cognition state (3.90±2.28 daily drugs;  $p<0.0001$ ).



**Figure 2.** The number of drugs daily consumption in older adults by cognitive status. Normal cognition group,  $n= 976$ ; Impaired cognition group,  $n=229$ . The statistical comparison was made by Test T. \*\*\*\*,  $p<0.0001$ . The bars represent the mean and SD.

Source: prepared by authors

## Discussion

In the study, was found that 19% of older adults presented cognitive impairment (Table 1), similar to the national level, according to the CASEN 2015 survey, in the population aged 60 years or older, cognitive impairment is prevalent at 17.5% (2). It is similar to Argentina where prevalence of 16.9%-18.3% is reported in older people (45). On the other hand, in a Mexican study carried out in the urban area of Guadalajara, a lower prevalence was found (11.9% - 16.0%) (46). Probably the age of the population studied in Mexican work influences these results (47.4% were less than 70 years old) that older people aged 70 years and over have a higher risk of cognitive impairment (47). In the study, the average age of older adults with cognitive impairment is 75.6 years.

The MMSE and other alternative tools can help detect subtle changes in cognitive function. Previous studies that investigated the relationships between physical frailty and cognitive decline have assessed global cognitive function using the MMSE. The MMSE is a quick and easy measure

that assesses seven areas of cognitive functioning. It was shown to have both good test-retest reliability (0.80–0.95) and acceptable sensitivity and specificity to detect mild to moderate stages of dementia (48,49). No significant difference was found between cognitive impairment and gender, unlike at the national level and in countries such as Argentina, Brazil, Mexico, Cuba, and Uruguay, where the probability of having a cognitive impairment is higher in females (50). Furthermore, in the study population, the group with cognitive impairment had less years of education. This is consistent with a recent study, which shows that more years of education decreases the risk of cognitive impairment (51).

A high prevalence of living alone is observed in the group with cognitive impairment compared to the group with normal cognition. One possible explanation could be that older adults who live alone are at increased risk for depression, and depression is known to increase the risk of cognitive impairment (52). In addition, there is no influence of the area of residence on cognitive impairment, which differs from that described in other studies, which report

a higher prevalence of cognitive impairment in rural areas (53,54). On the other hand, older people with cognitive impairment have a higher prevalence of frailty and polypharmacy, as seen in other studies (55,56). Recently, our team reported an increased prevalence of frailty regarding the progression of the state of polypharmacy, observing a frailty prevalence of 32.9% (CI 95%: 28.7-37.3) in older adults with polypharmacy conditions (43). Also, a frail state was found as a factor associated with polypharmacy in Chilean older adults (OR: 1.5, CI 95%: 1.1-2.2) (43).

Additionally, the study observed an association between cognitive impairment and frailty score (Figure 1). Similar results have been reported in other studies; a previous study done in the urban population of Santiago de Chile using the same definitions found a significant association between frailty and dementia (1.96;95%CI:1.23–0.11) but a tendency for cognitive impairment (OR=1.58;95%CI:0.97–2.59) (20). Robertson et al. (55) reported that frail and pre-frail people have impaired cognitive function (55). Another study reported that physical frailty is associated with an increased risk of mild cognitive impairment and a greater decline in cognitive function in older age (57). Chen et al. (58) also reported that frailty is associated with a cognitive decline in older adults over a period of two years (58). When analyzing the relationship between cognitive impairment and the Fried Frailty Criteria (24), a significant association was found between all criteria, except weakness criteria (Table 2). Other studies found a strong relationship between grip strength, slow gait speed, and low physical activity with cognitive decline (59,60). The relationship between cognitive impairment and frailty can partly be explained by recent evidence that both syndromes share common pathophysiological mechanisms (61,62). A recent work by Sargent et al. (26) analyzes both syndromes' common mechanisms (26). This machine-learning study shows that participants with cognitive frailty had higher inflammatory protein marker levels than healthy older adults, and among them, resistin protein (26). Resistin regulates interleukin-6, TNF, interleukin 1, and A2M, which are protease inhibitor cytokine transporters linked to Alzheimer's disease (63). In this sense, components of frailty were associated with pathological findings of Alzheimer's disease and vascular dementia, evidencing a possible common biological pathway between frailty and cognitive disorders (61,64).

The results also indicate that a high number of daily medications consumption is related to cognitive impairment. Polypharmacy is highly prevalent in older people and has been associated with an increased risk of mortality, adverse health events, unhealthy nutrition, and recently, an increased risk of cognitive impairment and

neurological diseases (32,33,65,66). Moreover, Alic et al. (56) found that adults over 65 who used three or more show a deterioration in cognitive abilities (56). Moreover, Trevisan et al. (65) suggest that mild polypharmacy (> 3 and <5 drugs/day) may increase the risk of progression from mild cognitive impairment to dementia (65). Consistent with the results, Moon et al. (21) reported an association between polypharmacy and cognitive impairment, being more likely to suffer from cognitive frailty (cognitive impairment and frailty) in the presence of polypharmacy (OR: 2.7) (21). However, more studies are needed to know which, combinations, doses, length of time prescribed and consumed might contribute to cognitive decline.

Finally, this study presents limitations and strengths. Since this study has a cross-sectional design, it is impossible to know the causes that explain the findings. Because of this, a longitudinal study would be necessary to evaluate the progression of frailty and the development of cognitive impairment. However, this study is robust due to the considerable number of participants and the extensive cohort characterization.

## Conclusions

The findings of the study show that older adults with cognitive impairment present advanced age, a lower educational level, and a high prevalence of living alone. Furthermore, the study concluded that a strong association exists between cognitive impairment and Fried frailty criteria (24), being the "exhaustion" criterion the most associated. This finding coincides with that reported in the literature, where it is shown that older adults with frailty have a higher risk of cognitive impairment. Also, the results show that older people with cognitive impairment present a higher consumption of medicines and, thus, a high prevalence of polypharmacy compared to older people with normal cognition; however, more studies are needed to evaluate which drugs or specific diseases are associated with cognitive impairment. Finally, the evidence presented suggests that the reduction of polypharmacy can be a real alternative for the prevention of cognitive damage, especially in frail older people.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Funding

This work has been funded by the Interuniversity Center for Healthy Aging, Code RED211993, ANID-FONDECYT N° 1211136, and ANID FONDECYT N°3230783.

## Ethical responsibilities

The Scientific Ethics Committee from the University of Talca approved the study (code 2016-019-IP). Informed consent was obtained from all subjects involved. All methods were carried out under relevant guidelines and regulations.

## References

1. World Health Organization. Informe Mundial sobre el envejecimiento y la salud [Internet]. Ginebra: WHO; 2015. Available from: <https://www.who.int/es/publications/i/item/9789241565042>
2. Ministerio de Desarrollo Social. Informe de Desarrollo Social [Internet]. Chile: Ministerio de Desarrollo Social; 2017. Available from: <https://www.desarrollosocialyfamilia.gob.cl/pdf/upload/IDS2017.pdf>
3. Instituto Nacional de Estadísticas. Chile: estimaciones y proyecciones de población por sexo, edad, total país: 1950-2050 [Internet]. Chile: INE-CEPAL; 1995. Available from: <https://repositorio.cepal.org/entities/publication/8e5d0343-636e-4a81-b59f-ec0d8511dcfb>
4. He W, Goodkind D, Kowal P. An Aging World: 2015. International Population Reports [Internet]. United States: United States Bureau; 2016. Available from: <https://www.census.gov/content/dam/Census/library/publications/2016/demo/p95-16-1.pdf>
5. Bektas A, Schurman SH, Sen R, Ferrucci L. Aging, inflammation and the environment. *Exp Gerontol* [Internet]. 2018;105:10-18. doi: <https://doi.org/10.1016/j.exger.2017.12.015>
6. Bademli K, Lok N, Canbaz M, Lok S. Effects of Physical Activity Program on cognitive function and sleep quality in elderly with mild cognitive impairment: A randomized controlled trial. *Perspect Psychiatr care* [Internet]. 2019;55(3):401-408. doi: <https://doi.org/10.1111/ppc.12324>
7. Chudiak A, Uchmanowicz I, Mazur G. Relation between cognitive impairment and treatment adherence in elderly hypertensive patients. *Clin Interv Aging* [Internet]. 2018;13:1409-18. doi: <https://doi.org/10.2147/CIA.S162701>
8. Degl'Innocenti A, Elmfeldt D, Hansson L, Breteler M, James O, Lithell H, et al. Cognitive function and health-related quality of life in elderly patients with hypertension--baseline data from the study on cognition and prognosis in the elderly (SCOPE). *Blood pressure* [Internet]. 2002;11(3):157-65. doi: <https://doi.org/10.1080/080370502760050395>
9. Christensen H, Jorm AF, Henderson AS, Mackinnon AJ, Korten AE, Scott LR. The relationship between health and cognitive functioning in a sample of elderly people in the community. *Age Ageing* [Internet]. 1994;23(3):204-12. doi: <https://doi.org/10.1093/ageing/23.3.204>
10. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review) [Retired]. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* [Internet]. 2001;56(9):1133-42. doi: <https://doi.org/10.1212/wnl.56.9.1133>
11. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. *Lancet* [Internet]. 2006;367(9518):1262-70. doi: [https://doi.org/10.1016/s0140-6736\(06\)68542-5](https://doi.org/10.1016/s0140-6736(06)68542-5)
12. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* [Internet]. 1975;12(3):189-98. doi: [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
13. Muñoz-Silva CA, Rojas-Orellana PA, Marzucan-Nassr GN. Criterios de valoración geriátrica integral en adultos mayores con dependencia moderada y severa en Centros de Atención Primaria en Chile. *Rev méd Chile* [Internet]. 2015;143(5):612-8. Available from: [https://www.scielo.cl/scielo.php?script=sci\\_arttext&pid=S0034-98872015000500009](https://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0034-98872015000500009)
14. Shim YS, Yang DW, Kim H-J, Park YH, Kim S. Characteristic differences in the mini-mental state examination used in Asian countries. *BMC Neurol* [Internet]. 2017;17(1):141. doi: <https://doi.org/10.1186/s12883-017-0925-z>
15. Arevalo-Rodriguez I, Smailagic N, Roqué-Figuls M, Ciapponi A, Sanchez-Perez E, Giannakou A, et al. Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev* [Internet]. 2015;2015(3):CD010783. doi: <https://doi.org/10.1002/14651858.cd010783.pub2>
16. Pais R, Ruano L, Carvalho OP, Barros H. Global Cognitive Impairment Prevalence and Incidence in Community Dwelling Older Adults-A Systematic Review. *Geriatrics (Basel)* [Internet]. 2020;5(4):84. doi: <https://doi.org/10.3390/geriatrics5040084>
17. Vega-Alonso T, Miralles-Espí M, Mangas-Reina JM, Castrillejo-Pérez D, Rivas-Pérez AI, Gil-Costa M, et al. Prevalence of cognitive impairment in Spain: The Gómez de Caso study in health sentinel networks. *Neurologia (Engl Ed)* [Internet]. 2018;33(8):491-8. doi: <https://doi.org/10.1016/j.nrl.2016.10.002>
18. Albala C, Lera L, Sanchez H, Angel B, Marquez C, Arroyo P, et al. Frequency of frailty and its association with cognitive status and survival in older Chileans. *Clin Interv Aging* [Internet]. 2017;12:995-1001. doi: <https://doi.org/10.2147/cia.s136906>
19. Prince MJ, Wu F, Guo Y, Gutierrez-Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. *Lancet* [Internet]. 2015;385(9967):549-62. doi: [https://doi.org/10.1016/s0140-6736\(14\)61347-7](https://doi.org/10.1016/s0140-6736(14)61347-7)

20. Barberger-Gateau P, Fabrigoule C. Disability and cognitive impairment in the elderly. *Disabil Rehabil* [Internet]. 1997;19(5):175-93. doi: <https://doi.org/10.3109/09638289709166525>
21. Moon JH, Huh JS, Won CW, Kim HJ. Is Polypharmacy Associated with Cognitive Frailty in the Elderly? Results from the Korean Frailty and Aging Cohort Study. *The journal of nutrition, health & aging*. 2019;23(10):958-65. Moon JH, Huh JS, Won CW, Kim HJ. Is Polypharmacy Associated with Cognitive Frailty in the Elderly? Results from the Korean Frailty and Aging Cohort Study. *J Nutr Health Aging* [Internet]. 2019;23(10):958-65. doi: <https://doi.org/10.1007/s12603-019-1274-y>
22. Gobbens RJ, Schols JM, van Assen MA. Exploring the efficiency of the Tilburg Frailty Indicator: a review. *Clin Interv Aging* [Internet]. 2017;12:1739-52. doi: <https://doi.org/10.2147/cia.s130686>
23. Alonso-Bouzon C, Carcaillon L, Garcia-Garcia FJ, Amor-Andres MS, Assar ME, Rodriguez-Mañas L. Association between endothelial dysfunction and frailty: the Toledo Study for Healthy Aging. *Age (Dordr)* [Internet]. 2014;36(1):495-505. doi: <https://doi.org/10.1007/s11357-013-9576-1>
24. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* [Internet]. 2001;56(3):M146-56. doi: <https://doi.org/10.1093/gerona/56.3.m146>
25. Sardella A, Catalano A, Lenzo V, Bellone F, Corica F, Quattropani MC, et al. Association between cognitive reserve dimensions and frailty among older adults: A structured narrative review. *Geriatr Gerontol Int* [Internet]. 2020;20(11):1005-23. doi: <https://doi.org/10.1111/ggi.14040>
26. Sargent L, Nalls M, Amella EJ, Slattum PW, Mueller M, Bandinelli S, et al. Shared mechanisms for cognitive impairment and physical frailty: A model for complex systems. *Alzheimers Dement (N Y)* [Internet]. 2020;6(1):e12027. doi: <https://doi.org/10.1002/trc2.12027>
27. Borges MK, Canevelli M, Cesari M, Aprahamian I. Frailty as a Predictor of Cognitive Disorders: A Systematic Review and Meta-Analysis. *Front Med (Lausanne)* [Internet]. 2019;6:26. doi: <https://doi.org/10.3389/fmed.2019.00026>
28. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment - A review of the evidence and causal mechanisms. *Ageing Res Rev* [Internet]. 2013;12(4):840-51. doi: <https://doi.org/10.1016/j.arr.2013.06.004>
29. Inglés M, Mas-Bargues C, Gimeno-Mallench L, Cruz-Guerrero R, García-García FJ, Gambini J, et al. Relation Between Genetic Factors and Frailty in Older Adults. *J Am Med Dir Assoc* [Internet]. 2019;20(11):1451-7. doi: <https://doi.org/10.1016/j.jamda.2019.03.011>
30. Pansarasa O, Pistono C, Davin A, Bordoni M, Mimmi MC, Guaita A, et al. Altered immune system in frailty: Genetics and diet may influence inflammation. *Ageing Res Rev* [Internet]. 2019;54:100935. doi: <https://doi.org/10.1016/j.arr.2019.100935>
31. Palmer K, Villani ER, Vetrano DL, Cherubini A, Cruz-Jentoft AJ, Curtin D, et al. Association of polypharmacy and hyperpolypharmacy with frailty states: a systematic review and meta-analysis. *Eur Geriatr Med* [Internet]. 2019;10(1):9-36. doi: <https://doi.org/10.1007/s41999-018-0124-5>
32. Vetrano DL, Villani ER, Grande G, Giovannini S, Cipriani MC, Manes-Gravina E, et al. Association of Polypharmacy With 1-Year Trajectories of Cognitive and Physical Function in Nursing Home Residents: Results From a Multicenter European Study. *J Am Med Dir Assoc* [Internet]. 2018;19(8):710-713. doi: <https://doi.org/10.1016/j.jamda.2018.04.008>
33. Umegaki H, Yanagawa M, Komiya H, Matsubara M, Fujisawa C, Suzuki Y, et al. Polypharmacy and gait speed in individuals with mild cognitive impairment. *Geriatr Gerontol Int* [Internet]. 2019;19(8):730-5. doi: <https://doi.org/10.1111/ggi.13688>
34. Rosted E, Schultz M, Sanders S. Frailty and polypharmacy in elderly patients are associated with a high readmission risk. *Dan Med J* [Internet]. 2016;63(9):A5274. Available from: <https://pubmed.ncbi.nlm.nih.gov/27585531/>
35. Bonaga B, Sanchez-Jurado PM, Martinez-Reig M, Ariza G, Rodriguez-Manas L, Gnjjidic D, et al. Frailty, Polypharmacy, and Health Outcomes in Older Adults: The Frailty and Dependence in Albacete Study. *J Am Med Dir Assoc* [Internet]. 2018;19(1):46-52. doi: <https://doi.org/10.1016/j.jamda.2017.07.008>
36. Herr M, Robine JM, Pinot J, Arvieu JJ, Ankri J. Polypharmacy and frailty: prevalence, relationship, and impact on mortality in a French sample of 2350 old people. *Pharmacoepidemiol Drug Saf* [Internet]. 2015;24(6):637-46. doi: <https://doi.org/10.1002/pds.3772>
37. Palomo I, Giacaman RA, León S, Lobos G, Bustamante M, Wehinger S, et al. Analysis of the characteristics and components for the frailty syndrome in older adults from central Chile. The PIEI-ES study. *Arch Gerontol Geriatr* [Internet]. 2019;80:70-5. doi: <https://doi.org/10.1016/j.archger.2018.10.004>
38. Albala-Brevis C, Icaza G, Vio F, García C, Marín PP, Quiroga P. A short test to evaluate cognitive impairment based on Folstein's MMSE. *Gerontology*. 2001;47(S1):S183.
39. Ministerio de Salud. Manual de Aplicación del Examen de Medicina Preventiva del Adulto Mayor. División de Prevención y Control de Enfermedades. Subsecretaría de Salud Pública [Internet]. Chile: Minsal; 2010. Available from: [https://diprece.minsal.cl/wrdprss\\_minsal/wp-content/uploads/2015/05/instructivo-de-control-de-salud-empam.pdf](https://diprece.minsal.cl/wrdprss_minsal/wp-content/uploads/2015/05/instructivo-de-control-de-salud-empam.pdf)

40. Noh B, Youm C, Lee M, Park H. Associating Gait Phase and Physical Fitness with Global Cognitive Function in the Aged. *Int J Environ Res Public Health* [Internet]. 2020;17(13):4786. doi: <https://doi.org/10.3390/ijerph17134786>
41. Lera L, Albala C, Leyton B, Marquez C, Angel B, Saguez R, et al. Reference values of hand-grip dynamometry and the relationship between low strength and mortality in older Chileans. *Clin Interv Aging* [Internet]. 2018;13:317-24. doi: <https://doi.org/10.2147/cia.s152946>
42. García-García FJ, Gutiérrez-Avila G, Alfaro-Acha A, Amor-Andres MS, De La Torre-Lanza MA, Escribano-Aparicio MV, et al. The prevalence of frailty syndrome in an older population from Spain. The Toledo Study for Healthy Aging. *J Nutr Health Aging* [Internet]. 2011;15(10):852-6. Doi: <https://doi.org/10.1007/s12603-011-0075-8>
43. Arauna D, Cerda A, García-García JF, Wehinger S, Castro F, Méndez D, et al. Polypharmacy Is Associated with Frailty, Nutritional Risk and Chronic Disease in Chilean Older Adults: Remarks from PIEI-ES Study. *Clin Interv Aging* [Internet]. 2020;15:1013-22. doi: <https://doi.org/10.2147/cia.s247444>
44. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol* [Internet]. 2012;65(9):989-95. doi: <https://doi.org/10.1016/j.jclinepi.2012.02.018>
45. Bartolini L. Deterioro cognitivo. Diagnosis [Internet]. 2019;16:27-35. Available from: <https://dialnet.unirioja.es/servlet/articulo?codigo=7221180>
46. Ortiz GG, Arias-Merino ED, Flores-Saiffe ME, Velazquez-Brizuela IE, Macias-Islas MA, Pacheco-Moises FP. Prevalence of Cognitive Impairment and Depression among a Population Aged over 60 Years in the Metropolitan Area of Guadalajara, Mexico. *Curr Gerontol Geriatr Res* [Internet]. 2012;2012:175019. doi: <https://doi.org/10.1155/2012/175019>
47. Saw YM, Saw TN, Than TM, Khaing M, Soe PP, Oo S, et al. Cognitive impairment and its risk factors among Myanmar elderly using the Revised Hasegawa's Dementia Scale: A cross-sectional study in Nay Pyi Taw, Myanmar. *PLoS One* [Internet]. 2020;15(7):e0236656. doi: <https://doi.org/10.1371/journal.pone.0236656>
48. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc* [Internet]. 1992;40(9):922-35. doi: <https://doi.org/10.1111/j.1532-5415.1992.tb01992.x>
49. Li A, Chen S, Liu J, Chen T, Shi Y. CSL-CTEA: a systematic method for evaluating novel intelligent cognitive assessment tools. *Health Inf Sci Syst* [Internet]. 2025;13(1):29. doi: <https://doi.org/10.1007/s13755-025-00346-6>
50. Ashby-Mitchell K, Jagger C, Fouweather T, Anstey KJ. Life expectancy with and without cognitive impairment in seven Latin American and Caribbean countries. *PLoS One* [Internet]. 2015;10(3):e0121867. doi: <https://doi.org/10.1371/journal.pone.0121867>
51. Makkar SR, Lipnicki DM, Crawford JD, Kochan NA, Castro-Costa E, Lima-Costa MF, et al. Education and the moderating roles of age, sex, ethnicity and apolipoprotein epsilon 4 on the risk of cognitive impairment. *Arch Gerontol Geriatr* [Internet]. 2020;91:104112. doi: <https://doi.org/10.1016/j.archger.2020.104112>
52. Lee J, Ham MJ, Pyeon JY, Oh E, Jeong SH, Sohn EH, et al. Factors Affecting Cognitive Impairment and Depression in the Elderly Who Live Alone: Cases in Daejeon Metropolitan City. *Dement Neurocogn Disord* [Internet]. 2017;16(1):12-19. doi: <https://doi.org/10.12779/dnd.2017.16.1.12>
53. Jia J, Wang F, Wei C, Zhou A, Jia X, Li F, et al. The prevalence of dementia in urban and rural areas of China. *Alzheimers Dement* [Internet]. 2014;10(1):1-9. doi: <https://doi.org/10.1016/j.jalz.2013.01.012>
54. Wang J, Xiao LD, Wang K, Luo Y, Li X. Gender Differences in Cognitive Impairment among Rural Elderly in China. *Int J Environ Res Public Health* [Internet]. 2020;17(10). doi: <https://doi.org/10.3390/ijerph17103724>
55. Robertson DA, Savva GM, Coen RF, Kenny RA. Cognitive function in the prefrailty and frailty syndrome. *J Am Geriatr Soc* [Internet]. 2014;62(11):2118-24. doi: <https://doi.org/10.1111/jgs.13111>
56. Alic A, Pranjić N, Ramić E. Polypharmacy and decreased cognitive abilities in elderly patients. *Med Arh* [Internet]. 2011;65(2):102-5. Available from: <https://pubmed.ncbi.nlm.nih.gov/21585185/>
57. Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *J Am Geriatr Soc* [Internet]. 2010;58(2):248-55. doi: <https://doi.org/10.1111/j.1532-5415.2009.02671.x>
58. Chen S, Honda T, Narazaki K, Chen T, Kishimoto H, Haeuchi Y, et al. Physical Frailty Is Associated with Longitudinal Decline in Global Cognitive Function in Non-Demented Older Adults: A Prospective Study. *J Nutr Health Aging* [Internet]. 2018;22(1):82-8. doi: <https://doi.org/10.1007/s12603-017-0924-1>
59. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology* [Internet]. 2012;78(17):1323-9. doi: <https://doi.org/10.1212/WNL.0b013e3182535d35>
60. Yassuda MS, Lopes A, Cachioni M, Falcao DV, Batistoni SS, Guimaraes VV, et al. Frailty criteria and cognitive performance are related: data from the FIBRA study in Ermelino Matarazzo, Sao Paulo, Brazil. *J Nutr Health Aging* [Internet]. 2012;16(1):55-61. doi: <https://doi.org/10.1007/s12603-012-0003-6>

61. Buchman AS, Yu L, Wilson RS, Boyle PA, Schneider JA, Bennett DA. Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. *J Gerontol A Biol Sci Med Sci* [Internet]. 2014;69(12):1536-44. doi: <https://doi.org/10.1093/gerona/glu117>
62. Searle SD, Rockwood K. Frailty and the risk of cognitive impairment. *Alzheimers Res Ther* [Internet]. 2015;7(1):54. doi: <https://doi.org/10.1186/s13195-015-0140-3>
63. Kızıllarslanoğlu MC, Kara Ö, Yeşil Y, Kuyumcu ME, Öztürk ZA, Cankurtaran M, et al. Alzheimer disease, inflammation, and novel inflammatory marker: resistin. *Turk J Med Sci* [Internet]. 2015;45(5):1040-6. Available from: <https://pubmed.ncbi.nlm.nih.gov/26738345/>
64. Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. *Psychosom Med* [Internet]. 2007;69(5):483-9. doi: <https://doi.org/10.1097/psy.0b013e318068de1d>
65. Trevisan C, Limongi F, Siviero P, Noale M, Cignarella A, Manzato E, et al. Mild polypharmacy and MCI progression in older adults: the mediation effect of drug-drug interactions. *Aging Clin Exp Res*. 2021;33(1):49-56. doi: <https://doi.org/10.1007/s40520-019-01420-2>
66. Morin L, Johnell K, Laroche ML, Fastbom J, Wastesson JW. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. *Clin Epidemiol* [Internet]. 2018;10:289-98. doi: <https://doi.org/10.2147/clep.s153458>