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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

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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 ± 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 ± 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; Geriatría

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 ± 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 ≤ 13 was considered altered cognition, and a score ≥ 14 was normal cognition. With this cut-off point, was stratified the cohort into two groups: normal cognition (score ≥ 14 in MMSE) and altered cognition (score ≤ 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 Gnjdjic 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 ± 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 ± 6.5 years old) compared to the normal cognition group (72.7 ± 5.6 years old; $p < 0.0001$). Also, the altered cognition group had a shorter education (5.9 ± 4.0 years) compared to the normal cognition group (7.2 ± 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)]	73.0 ± 5.9	72.7 ± 5.6	75.9 ± 6.5	<0.0001
Years of Education [Mean (SD)]	7.2 ± 4.4	7.5 ± 4.4	5.9 ± 4.0	<0.0001
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)	<0.0001
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)	<0.0001
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 ± 1.45) than those without cognitive impairment (1.18 ± 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.

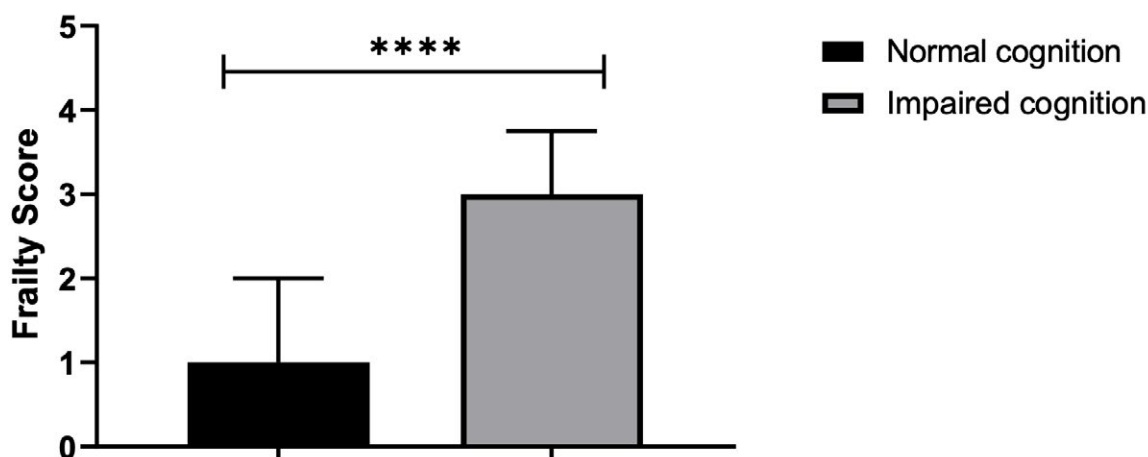


Figure 1. Frailty score in older adults with and without cognitive impairment. Normal cognition group, n=976; Impaired cognition group, n=229. The statistical comparison was made by the Whitney Test. ****, p<0.0001. The bars represent the median and interquartile range.

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; $p < 0.0001$).

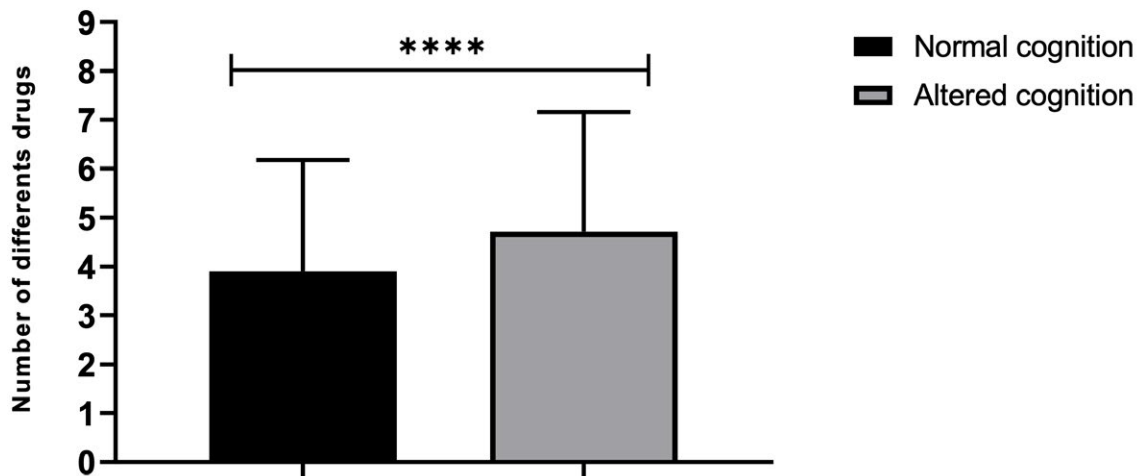


Figure 2. The number of drugs daily consumption in older adults by cognitive status. Normal cognition group, n= 976; Impaired cognition group, n=229. The statistical comparison was made by Test T. ****, $p < 0.0001$. The bars represent the mean and SD.

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.

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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.

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