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IS POLYPHARMACY ASSOCIATED WITH COGNITIVE FRAILTY IN THE ELDERLY? RESULTS FROM THE KOREAN FRAILTY AND AGING COHORT STUDY

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Abstract: *Objectives:* Cognitive frailty—the coexistence of physical frailty and cognitive impairment—is a phenotype of frailty in the elderly. The coexistence of physical frailty and cognitive impairment, known as cognitive frailty, is one of the phenotypes of frailty in the elderly. Cognitive frailty predicts adverse health outcome more accurately than does physical frailty. In this study, we aim to determine whether the polypharmacy common among the elderly is linked with cognitive frailty. *Design, Setting, and Participants:* The elderly, aged between 70 and 84 years, who participated in the cross-sectional Korean Frailty and Aging Cohort Study were included in the present study. *Measurements:* Polypharmacy and hyperpolypharmacy were defined as the use of at least five and ten medications, respectively. Physical frailty was assessed by the Korean version of the FRAIL scale, and cognitive status was measured by the Trail Making Test part A, word list recall test, the Korean version of the Frontal Assessment Battery, and the Digit Span Backward test. *Results:* Among the 2,392 participants, 26.8% and 4.1% took more than five and ten prescribed medications, respectively. Polypharmacy and hyperpolypharmacy participants tend to have more cognitive impairment and physical frailty. Participants with cognitive frailty had the highest polypharmacy rate regardless of medication type. After controlling for the potential confounders including severity of comorbidities, frailty was found to be significantly related to polypharmacy, as defined by prescribed as well as total medications, including non-prescribed medications. However, cognitive impairment only showed a linkage to polypharmacy of prescribed medications, which—according to the results of multivariable analysis— could increase cognitive frailty, with an odds ratio of 2.70. *Conclusion:* Although the elderly tend to depend on various medications, they should seriously consider the risk of polypharmacy for better health outcomes.

Key words: Polypharmacy, elderly, geriatric syndromes, frail, cognition, cognitive frailty.

Introduction

As age increases, so do the number of health-related comorbidities, causing the elderly to take multiple medications. As a result, polypharmacy, a geriatric syndrome, is fairly common among the elderly. The problem is that polypharmacy may lead to inappropriate drug use and drug–drug or drug–disease interactions. Furthermore, polypharmacy is linked with other geriatric syndromes, such as falls (1) and physical impairment (2), eventually necessitating further medication for the elderly. Prolonged exposure to multiple medications can cause new comorbidities, thus perpetuating a vicious cycle.

As the vicious cycle repeats, the elderly become frail (3). Physical frailty, characterized by diminished strength and endurance caused by decreased homeostatic reserve, is a common phenomenon among the elderly. Frailty is linked with adverse health outcomes including falls and functional dependence, which increase the risk of mortality (4). Furthermore, according to current epidemiologic studies, physical frailty and cognitive impairment, both of which are common among the elderly, are closely related (5,6). They share multiple pathophysiological mechanisms as well as clinical and subclinical factors. Increased interleukin 6, decreased DHEA and vitamin D, anemia, and white matter hyperdensities have been seen in studies on frailty and Alzheimer's disease (7). Furthermore, obesity, low physical activity, low educational level, smoking, and high alcohol consumption negatively affect brain aging and physical frailty (8). The frail elderly usually also tend to have cognitive impairment, and the concurrence of physical frailty and cognitive impairment is called cognitive frailty (9). It raises the risk for incident neurocognitive disorder (10) and improves the predictive validity for adverse health outcomes (11). A longitudinal study of a large population of those aged 65 and older without dementia indicated that frailty increased the risk for developing non-Alzheimer' disease dementia by 2.57 times (12). According to an Italian study, cognitive frailty among individuals is closely linked to disability (13), and in a longitudinal study conducted in Taiwan, the prevalence of cognitive frailty was 8.6%, raising the all-cause mortality risk threefold(14). Hence, cognitive frailty is one of the frailty phenotypes included in the comprehensive assessment of the

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elderly that more accurately predicts poor outcomes.

It is crucial to assess cognitive frailty and identify its risk factors to prevent poor future health outcomes among the elderly. Polypharmacy, a widespread phenomenon among the elderly, could be one of the risk factors for cognitive frailty. In this study, we sought to determine whether polypharmacy is related with physical frailty, cognitive impairment, and cognitive frailty in the community-dwelling elderly who were enrolled in the Korean Frailty and Aging Cohort Study (KFACS).

Methods

Study population

The KFACS, a nationwide cohort study conducted since 2016, aims to identify the adverse health outcomes and preventive factors related to frailty in the community-dwelling elderly. Elderly individuals aged between 70 and 84 years were recruited from 10 centers across Korean urban, agricultural, and rural countryside communities, based on age- and gender-specific strata (15). Well-trained interviewers conducted in-person interviews and performed health examinations. Written informed consent was provided by all participants.

Our study was based on data from the KFACS performed in 2016 and 2017. A total of 3,014 persons participated in the baseline survey, of which 173 participants were excluded due to missing data on frailty, cognitive impairment, and medication questionnaires. Participants who were dependent on others for instrumental activities of daily living (IADL) were also excluded from this study to assess cognitive frailty. Finally, a total of 622 participants were excluded; the remaining comprised 1,123 men and 1,269 women.

Polypharmacy and hyperpolypharmacy

Trained investigators checked the prescriptions that the participants had at home and the medications that they bought. Of these medications, only those that were taken for more than three months were recorded and classified as prescribed or non-prescribed medication. In line with previous studies, polypharmacy and hyperpolypharmacy were defined as five (16) and ten medications (17) or more per person, respectively, taken for more than three months. In this study, we analyzed polypharmacy and hyperpolypharmacy based on prescribed as well as non-prescribed medications.

Physical frailty

Morley et al. (18) proposed the FRAIL scale, a simple five-item questionnaire, which has been validated in Asian countries. In this study, physical frailty was assessed using the Korean version of the FRAIL (K-FRAIL) scale (19). Several recent epidemiologic studies have used the K-FRAIL scale (20,21). It comprises the following five items:

1. Fatigue: this was assessed by the question "Have you ever felt tired during the last month?" When participants answered "all of the time" or "most of the time," they received a score of one point.

2. Resistance: this was evaluated by the question "Do you have any difficulty in climbing 10 stairs without resting on your own and without the aid of others?"

3. Ambulation: this difficulty was defined based on participants' answers to the question "Is it hard to move 300 meters alone without help?"

4. Illnesses: these were defined as five more diseases out of eleven—hypertension, diabetes mellitus, chronic obstructive pulmonary disease, angina, myocardial infarction, heart failure, asthma, arthritis, stroke, renal disease, and cancer.

5. Weight loss: this was identified by asking participants whether they lost at least 5% of their body weight in the preceding year.

The combined scores on each item were classified to indicate participants' overall health status as follows: frail (3–5), prefrail (1–2), and robust (0).

Cognitive impairment and cognitive frailty

All participants received a comprehensive cognitive assessment, including the Trail Making Test part A to determine psychomotor speed, attention, sequencing, and visual scanning. Participants' dysexecutive syndrome, attention, and memory function were evaluated using the Frontal Assessment Battery, Digit Span Backward test, and a Word List Recall test, respectively. The Korean version of the Trail Making Test part A and the Word List Recall test were tested using the Korean version of the consortium to establish a registry for Alzheimer's disease assessment packet (22, 23). Furthermore the Korean version of the Frontal Assessment Battery (24), and the Korean normative study of the Digit Span were used to evaluate the cognitive status of the participants (25). Participants without deficits in the four tests were assessed as cognitively intact, while those with cognitive impairment were assessed as being more than 1.5 standard deviations below the mean for age-, gender-, and education-adjusted Korean norms on any of the above cognitive function tests (26). Cognitive frailty was defined as the concomitant presence of physical frailty and cognitive impairment. Participants were categorized into the following six groups: physically robust without cognitive impairment, physically robust with cognitive impairment, physically prefrail without cognitive impairment, physically prefrail with cognitive impairment, physically frail without cognitive impairment, and physically frail with cognitive impairment.

Other variables

Comprehensive in-person interviews and functional examinations were performed, and participants' sociodemographic characteristics, health behaviors, activities of daily living, and IADL were evaluated. Moreover, comorbidities that are highly correlated with the number of medications being taken were also evaluated, and the Charlson

Table 1
Baseline characteristics of the study population by the number of prescribed medications

	Non-polypharmacy (n=1652)	Polypharmacy (n=642)	Hyper-polypharmacy (n=98)	P for trend
Age (yr)	75.50±3.80	76.57±3.84	76.66±4.04	<0.001
Gender (women)	910 (55.1)	318 (49.5)	41 (41.8)	0.001
Education (yr)	9.04±5.30	8.83±5.24	8.42±4.81	0.180
Body mass index (kg/m2)	24.22±2.91	24.97±3.09	24.92±3.21	<0.001
Activities of daily living	7.08±0.28	7.10±0.30	7.07±0.25	0.272
Instrumental activities of daily living	11.43±2.84	11.79±3.11	11.83±3.21	0.004
Mini nutritional assessment score	12.94±1.39	12.85±1.57	12.52±2.02	0.009
Geriatric depression scale score	2.78±3.41	3.46±3.75	3.89±3.75	<0.001
Charlson comorbidity score	0.34±0.70	0.83±0.88	1.07±1.06	<0.001
Comorbities				
Stroke	46 (2.8)	49 (7.6)	11 (11.2)	<0.001
Myocardiac infarction	16 (1.0)	28 (4.4)	8 (8.2)	<0.001
Hypertension	810 (49.0)	472 (73.5)	75 (76.5)	<0.001
Diabetes	214 (13.0)	249 (38.8)	49 (50.0)	<0.001
Low muscle mass[1]	593 (36.0)	217 (33.9)	34 (34.7)	0.404
Decreased grip strength[2]	237 (14.3)	144 (22.4)	28 (28.6)	<0.001
Decreased funtional mobility[3]	682 (41.3)	350 (54.6)	65 (67.0)	<0.001
Low physical activity[4]	117 (7.1)	83 (12.9)	18 (18.4)	<0.001
Cognitive impairment	298 (18.0)	139 (21.7)	27 (27.6)	0.005
Trail making test	54 (3.3)	29 (4.5)	7 (7.1)	0.027
Frontal assessment battery	118 (7.1)	49 (7.6)	5 (5.1)	0.858
Digit span backward	143 (8.7)	66 (10.3)	13 (13.3)	0.072
Word list recall test	54 (3.3)	31 (4.8)	6 (6.1)	0.033
K-FRAIL component				
Fatigue	370 (22.4)	1901 (29.6)	39 (39.8)	<0.001
Resistance	595 (36.0)	310 (48.3)	56 (57.1)	<0.001
Ambulation	1378 (83.4)	481 (74.9)	67 (68.4)	<0.001
Illnesses	27 (1.6)	26 (4.0)	5 (5.1)	<0.001
Loss of weight	120 (7.3)	54 (8.4)	20 (20.4)	<0.001
K-FRAIL status				<0.001
Robust	814 (49.3)	242 (37.7)	23 (23.5)	
Prefrail	693 (41.9)	298 (46.4)	52 (53.1)	
Frail	145 (8.8)	102 (15.9)	23 (23.5)	

Values are presented as mean ± standard deviation or number (%). Comparison between three groups was done by oneway analysis of variance test and Jonckheere Terpstra test or chi-square test. [1,2] Low muscle mass and decreased grip strengh used herein were that of the Asian Working Group for Sarcopenia. [3] Defined as timed Up and Go test over 10 seconds. 4Defined as international physical activity questionnaire < 494.65 kcal for men and < 283.50 kcal for women.

Table 2
Characteristics of the participants according to physical frailty and cognitive impairment status

	Robust without cognitive impairment (n=906)	Robust with cognitive impairment (n=173)	Prefrail without cognitive impairment (n=829)	Prefrail with cognitive impairment (n=214)	Frail without cognitive impairment (n=193)	Frail with cognitive impairment (n=77)	P-value
Age (yr)	74.93±3.57[a]	75.88±3.82[b]	76.00±3.88[b]	76.40±3.76[b]	77.90±3.94[c]	77.86±3.56[c]	<0.001
Gender (women)	402 (44.4)	59 (34.1)	509 (61.4)	104 (48.6)	147 (76.2)	48 (62.3)	<0.001
Education (yr)	10.41±4.60[a]	10.14±4.53[a]	8.44±4.48[b]	7.96±4.94[b]	5.48±4.30[c]	6.23±11.58[c]	<0.001
Body mass index (kg/m^2)	24.42±2.73	24.28±2.63	24.55±3.11	24.29±3.07	24.56±3.72	24.19±3.24	0.690
Low physical activity	40 (4.4)	9 (5.2)	83 (10.0)	25 (11.7)	41 (21.2)	20 (26.0)	<0.001
Activities of daily living	7.06±0.24[a]	7.06±0.25[a]	7.09±0.29[a]	7.07±0.27[a]	7.19±0.42[b]	7.16±0.41[b]	<0.001
Instrumental activities of daily living	11.77±3.07[a,b]	12.28±3.36[a]	11.22±2.70[b]	11.72±3.18[a,b]	10.93±2.26[b]	11.71±2.97[a,b]	<0.001
Charlson comorbidity score	0.43 0.73[a]	0.38±0.71[a]	0.54±0.84[a,b,c]	0.51±0.89[a,b]	0.65±0.93[b,c]	0.70±0.87[c]	<0.001
Number of medications (prescribed medications)	2.90±2.57[a]	3.16±2.96[a,b]	3.71±2.97[b]	3.75±3.21[b]	4.58±3.03[c]	4.97±3.47[c]	<0.001
Number of medications (prescribed and non-prescribed medications)	3.84±2.86[a]	3.89±3.26[a]	4.65±3.19[a,b]	4.39±3.31[b]	5.31±3.23[c]	5.35±3.57[c]	<0.001

Statistical significances were test by oneway analysis of variances among groups. The same letters indicate non-significant difference between groups based on Ducan multiple comparison test.

Comorbidity Index to assess the severity of comorbidities was calculated (27). Nutritional status was assessed using the Korean version of the Mini Nutritional Assessment-Short Form (28), and the mood of participants was evaluated using the Korean version of the Geriatric Depression Scale Short Form (29). Muscle mass was measured using dual-energy X-ray absorptiometry (Lunar, GE Healthcare, Madison, WI, USA; and Hologic DXA, Hologic Inc., Bedford MA, USA) and bioelectrical impedance analysis (InBody 720, InBody Co., Ltd., Seoul, Korea; and X-SCAN PLUS II, Jawon Medical Inc., Seoul, Korea). Low muscle mass was defined by the Asian Working Group for Sarcopenia (30). Hand grip strength was measured using a digital hand grip gauge (Takei TKK 5401, Takei Scientific Instruments, Tokyo, Japan). A maximal value less than 26kg for men and 18 kg for women was defined as decreased grip strength (30). Physical performance was assessed using the Timed Up and Go Test, which, if it exceeded 10 seconds, was evaluated as a functional mobility problem (31). Physical activity was evaluated by scores derived using the International Physical Activity Questionnaire. The cut-off for low physical activity was 494.65 kcal for men and 283.50 kcal for women, which comprised the lower 20% of the Korean survey of older adults (32).

Statistical analysis

To compare baseline characteristics according to the polypharmacy and cognitive frailty status, we conducted an analysis of variance (ANOVA) with a post hoc analysis using the Ducan multiple comparison test and the Jonckheere Terpstra test for continuous variables and the chi-square test for categorical variables. The results are described as mean ± standard deviation (SD) or number (%) according to the characteristics of the variables. The relation between polypharmacy status, which was defined by prescribed and non-prescribed medications, and physical frailty and cognitive impairment were analyzed. Furthermore, the association of the status of medication and cognitive frailty was analyzed by multivariable logistic regression. Factors known to affect the increased risk of physical frailty and cognitive impairment were adjusted. Statistical analyses were per¬formed using IBM SPSS Statistics 23.0 (SPSS, International Business Machines Corp., Armonk, NY). The level of statistical significance in this study was defined by a value of P-value < 0.05.

Results

Sample characteristics according to the polypharmacy status

Baseline characteristics for participants according to the number of prescribed medications are shown in Table 1. Of the total 2,392 participants, 642 (26.8%) were taking more than five prescribed medications (polypharmacy) and 98 (4.1%) were taking more than ten prescribed medications (hyperpolypharmacy). Participants who took the most number of medications were taking 19 regular medications. The hyperpolypharmacy group comprised participants who were older than those in other groups; however, there was no significant difference in activities of daily living among the three groups. The frequency of hypertension, diabetes, stroke, and myocardial infarction as well as the Charlson Comorbidity Index were higher in the group taking more medications. There were a higher number of participants with cognitive impairment in the Trail Making Test and the Word List Recall test in

Table 3
Odds ratio of physical frailty and cognitive impairment status by polypharmacy

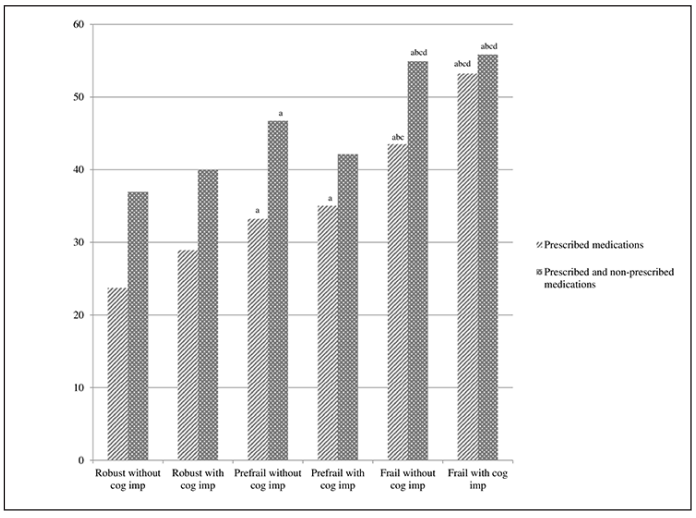
	Polypharmacy			
	≥5 Prescribed medications		≥5 Prescribed and non-prescribed medications	
	OR (95% CI)	p-value	OR (95% CI)	p-value
KFRAIL status				
Robust (n=1079)	Ref.		Ref.	
Prefrail (n=1043)	1.45 (1.17-1.79)	0.001	1.33 (1.09-1.61)	0.004
Frail (n=270)	1.93 (1.34-2.75)	<0.001	1.59 (1.13-2.23)	0.007
Cognitive impairment				
Normal cognition (n=1928)	Ref.		Ref.	
Impaired cognition (n=464)	1.27 (1.01-1.59)	0.045	1.04 (0.83-1.30)	0.697

CI=95% confidence intervals; Odds ra1.tio adjusted for age, gender, body mass index, years of education, Charlson comorbidity score, and low physical activity.

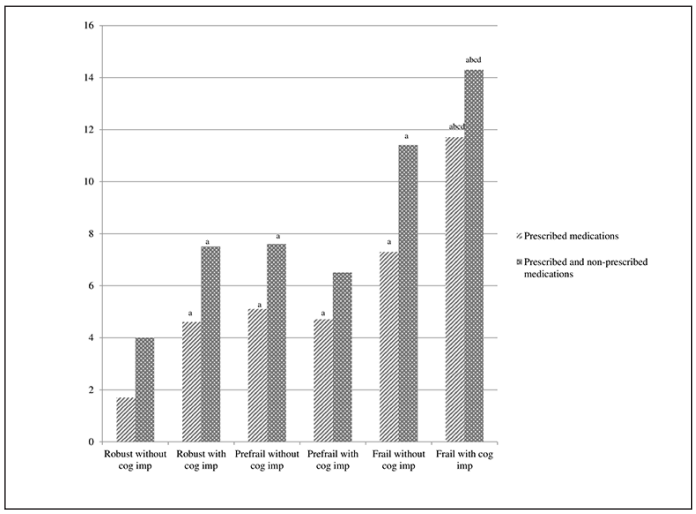
the hyperpolypharmacy group, but the results of the Frontal Assessment Battery and Digit Span Backward were not related to the number of medications. Cognitive impairment, defined as any impairment in the above four tests, was higher in the groups of participants who took more medications. The components of K-FRAIL—fatigue, resistance, ambulation, illnesses, and weight loss—showed a significant positive relation with the polypharmacy status, and the highest number of participants with hyperpolypharmacy were physically frail.

Figure 1
The rate of polypharmacy and hyperpolypharmacy according to the cognitive frailty status. Cog imp, cognitive impairment.

A) Polypharmacy



B) Hyperpolypharmacy



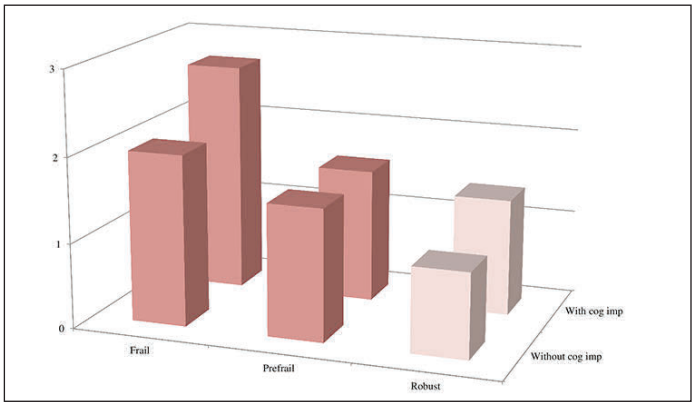
a. Significantly different from physically robust without Cog Imp group. b. Significantly different from physically robust with Cog Imp group. c. Significantly different from prefrail without Cog Imp group. d. Significantly different from prefrail with Cog Imp group

Sample characteristics according to physical frailty with cognitive impairment status

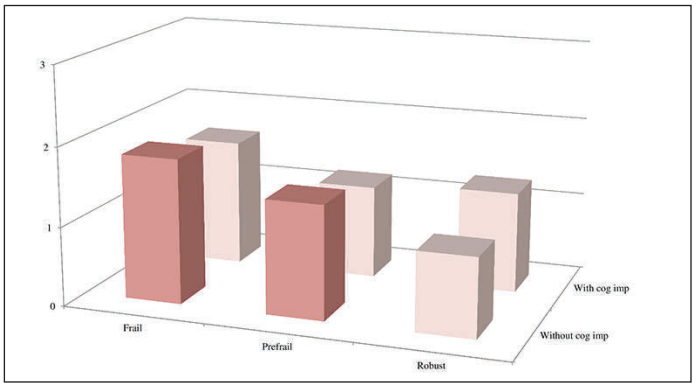
Regardless of cognitive status, frail participants were more aged and less educated. Body mass index (BMI) did not show a significant association with frailty and cognitive status. However, the Charlson Comorbidity Index was higher among the physically frail with cognitive impairment group. The number of prescribed and total medications including non-prescribed medication was higher in the frail groups regardless of cognitive status. In participants who were physically frail with cognitive impairment, the mean number of prescribed medications was 4.97 and the total number of medications was 5.35. These results are presented in Table 2.

Figure 2
Multivariate logistic regression analysis for the combined effect of frailty and cognitive impairement on polypharmacy. Cog imp, cognitive impairment

A) ≥ 5 prescribed medications



B) ≥ 5 prescribed and non-prescribed medications



a. Odds ratio adjusted for age, gender, body mass index, years of education, Charlson comorbidity score, and low physical activity. Light color : not significantly differecnt from 1, deep color: significant increase in risk

Polypharmacy with physical frailty and cognitive impairment

We analyzed the relationship between polypharmacy and physical frailty as well as cognitive impairment after adjusting for age, gender, BMI, years of education, Charlson Comorbidity Index, and low physical activity, and these results are shown in Table 3. Regardless of whether or not they were prescribed, taking more than five medications was meaningfully related with physically prefrail and frail statuses. The odds ratio (OR) of frailty in participants taking more than five prescribed medications and more than five total medications are 1.93 (95% confidence interval (CI): 1.34–2.75) and 1.59 (95% CI: 1.13–2.23), respectively. Polypharmacy defined by prescribed medication also showed a significant relation to cognitive impairment (OR=1.27, 95% CI: 1.01–1.59).

Polypharmacy with cognitive frailty

Fig 1 depicts the polypharmacy and hyperpolypharmacy of participants taking prescribed and total medications according to their cognitive impairment with frailty status. Compared with the physically robust without cognitive impairment group, polypharmacy rates were significantly higher in all other groups, regardless of the type of medication (all P-value < 0.001). The physically frail with cognitive impairment group showed significant higher polypharmacy frequency of prescribed and total medications than did the physically robust or physically prefrail groups, regardless of cognitive status (all P-value < 0.005). A similar association was found between the polypharmacy of total medication and the physically frail without cognitive impairment group (P-value < 0.005). This trend was also seen in hyperpolypharmacy regardless of prescribed or total medications including prescribed and non-prescribed medications (all P-value < 0.005).

We conducted a multivariate logistic regression analysis to determine the combined effect of frailty and cognitive impairment on polypharmacy. The results of the prescribed medication are presented in Fig 2 (A) while those of the total medications are presented in Fig 2 (B). After adjusting for the age, gender, BMI, years of education, Charlson Comorbidity Index, and low physical activity, physically prefrail and frail statuses, regardless of the cognitive status, were found to be significantly related with polypharmacy of prescribed medication. The OR of the physically prefrail without cognitive impairment was 1.55 (95% CI: 1.22–1.95), and that of the physically prefrail with cognitive impairment was 1.57 (95% CI: 1.09–-2.25). This tendency increased among frail participants. After adjusting for potential confounding variables, the OR of the physically frail without cognitive impairment was 2.01 (95% CI: 1.31–3.06) and that of the physically frail with cognitive impairment was 2.70 (95% CIL 1.51–4.80). In the analysis of total medications, there was a significant relation with participants who were classified as physically prefrail without cognitive impairment and frail without cognitive impairment, with the OR being 1.44 (95% CI: 1.16-1.78) and 1.83 (95% CI: 1.22-2.71), respectively. However, there were no associations between polypharmacy defined by total medications and cognitive impairment, regardless of physical status.

Discussion

In this study of community-dwelling elders aged between 70 and 84 years, we found that participants with polypharmacy and hyperpolypharmacy who took prescribed medications tended to have cognitive and physical frailty. Moreover, participants who took five or more prescribed medications had a significantly higher risk of physically frailty, cognitive impairment, and cognitive frailty after comprehensive adjustment.

Until now, many researchers have studied frailty and cognitive impairment separately. This trend is has been seen for polypharmacy as well. Many cross-sectional and longitudinal studies report a similar link between polypharmacy and cognitive impairment as does this study. Cognitive impairment, as defined by the Mini-Mental State Examination (MMSE), is significantly associated with polypharmacy, which was defined as the consumption of six or more prescribed medications among the community dwelling elderly in Japan (33). The results of a study on elderly nursing home residents are similar to the findings of our study. The elderly in long-term care facilities showed a high prevalence of polypharmacy with potentially inappropriate medications, and it is related with cognitive function (34). From one case-control study of 7,135 individuals with dementia and 28,540 control group individuals without dementia, the number of medications used increased with a corresponding increase in the risk of dementia (35). Like this study, many others report the close linkage between polypharmacy and frailty in the elderly. In a three-year follow-up study, polypharmacy (use of five or more medications) and hyperpolypharmacy (use of ten or more medications) increased to 2.30 and 4.79, respectively, in terms of the risk of frailty, defined by using a modified version of Fried frailty phenotype. Furthermore, the number of medications and the incidence of frailty are related (36). According to a cohort study in Australia, the risk of transitioning from robust to prefrail and from prefrail to frail increases by increasing the number of medications (37).

Our study corroborates prior findings that polypharmacy increases frailty and cognitive impairment. Not only this, this study appears to prove that polypharmacy increases the risk of those with coexisting physical frailty and cognitive impairment than of those with only one of these conditions. Previous studies on adverse outcomes of cognitive frailty showed a trend similar to that seen in our study. Physical frailty and cognitive impairment are linked with IADL limitations, and participants with cognitive frailty were most likely to experience a decline in IADL (38). Furthermore, in a Japanese study, participants with cognitive frailty showed a higher risk of dementia than did the elderly with frailty or cognitive impairment alone (39).

Interestingly, participants who are physically frail tend to have significantly fewer non-prescribed medications than do those who are of pre-frail or robust status, regardless of their cognitive status. Furthermore, cognitively frail participants were found to take the least number of non-prescribed medications. The cognitively frail elderly are more likely to be burdened with taking additional non-prescribed medications because they already take several prescribed medications for their morbidities. Although the total number of medications used was the highest among the cognitively frail participants, the relationship between polypharmacy evaluated by total medications and health outcomes was not clearly observed as compared to polypharmacy evaluated by prescribed medications.

This study has several strengths. The participants of KFACS are community-dwelling elderly aged 70 or more, and these participants are more vulnerable to frailty than the relatively younger elderly. Moreover, investigators have a high degree of accuracy because they directly checked prescription as well as non-prescription medications. The international Consensus Group on Cognitive Frailty by IANA and IAGG has already suggested comprehensive cognitive assessments including memory performance and other cognitive functions like executive functions (9). As to the cognitive assessment, previous studies tended to use the MMSE due to the speed of the test. However, the MMSE showed only 66.01% of sensitivity for mild cognitive impairment (MCI) (40). We believe that the MCI as well as pre-MCI phase is very important for reducing the incidence of dementia. Hence we conducted comprehensive cognitive function tests rather than the MMSE test to avoid missing MCI.

However, there are a few caveats when interpreting these results. First of all, because this study employed a cross-sectional design, we could not establish the cause–effect relationship between polypharmacy and cognitive frailty. Previous studies suggest that polypharmacy and cognitive frailty interact bidirectionally and form a vicious cycle; thus, breaking this cycle is very important. The prevalence of frailty among the elderly in the Asian-Pacific region was reported as 3.5–27% depending on where the studies were conducted (41). On the other hand, the prevalence of frailty among 1,318 participants in the first year of KFACS was 2.5–12.4% according to the different frailty scales (42). Participants of this study could have undergone several physical examinations, were perhaps healthier than the general population, and the prevalence of frailty might have been underestimated. In our study, we could not consider the kinds of medications or obtain the anatomical therapeutic chemical class code. Therefore, we could not evaluate potentially inappropriate medications or adverse drug reactions. However, regardless of the type of medications, there is an increased likelihood that interactions will occur as the number of drugs increases. Although there are various methods and concepts that have defined frailty, in this study, we used the K-FRAIL to assess frailty. According to a previous report, the K-FRAIL showed similar predictive value for mortality and disability assessed by the frailty index (43). Furthermore, the prevalence of frailty in first year of the KFACS assessed by the K-FRAIL was 12.4%, while the frailty index was 11.2% as defined by a cardiovascular health study (42). However, because there is no established diagnostic method for frailty and because various criteria used to assess frailty have their own strengths, it is necessary to evaluate frailty through various ways.

Conclusion

This study first analyzed the relationship between polypharmacy and cognitive frailty among the Korean elderly. Although it is not easy to avoid polypharmacy in elderly

people with multiple comorbidities, reducing the number of medicines consumed is necessary in conjunction with reducing the likelihood of adverse events including cognitive frailty. Considering that polypharmacy and cognitive frailty are common and pestilent phenomena in the elderly, our study is encouraging; however, future longitudinal studies are needed to identify causal mechanisms.

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Ethical standards: This study was approved by the Institutional Review Board of Jeju University Hospital (approval number: JEJUNUH 2016-03-008) and complied with the tenets of the Declaration of Helsinki.

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