Polypharmacy, Cognitive Impairment, and Frailty in the Women's Health and Aging Study II (WHASII)

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ABSTRACT:

Background: The population of adults over the age of 65 will make up 23% of the United States by year 2060 and will exceed the total population under age 18 for the first time by year 2034 (1). This group is at higher risk of experiencing cognitive impairment or frailty along with other comorbid conditions (2). It is common for older adults to be exposed to polypharmacy, such as the use of multiple prescription medications, in order to manage multiple chronic conditions (3-5). This analysis aims to characterize the effect of polypharmacy on the incidence of cognitive impairment and frailty in initially healthy women aged 70 and older.

Methods: This analysis looked at 284 community-dwelling women ages 70-80 from the WHAS II which was a prospective cohort study consisting of 436 women followed over an 11-year period. Women who were initially frail or cognitively impaired at baseline were removed from the analytic population as were those with stroke or Parkinson's disease who were predisposed to develop cognitive impairment and frailty. Multivariable Cox proportional hazards models were used to investigate the relationship between polypharmacy and outcomes of all-cause mortality, cognitive impairment, and frailty. The Fine and Gray competing risks model was used to assess the association between polypharmacy and patterns of occurrence of cognitive impairment and frailty accounting for each outcome as competing events.

Results: Of the 284 community-dwelling women from the WHAS II free of frailty and cognitive impairment at baseline, 119 developed cognitive impairment first, 21 developed frailty first, 11 developed both simultaneously, and 8 experienced death free of cognitive impairment (CI) or frailty. The remaining 133 were event-free for the duration of the study. Older women had a higher risk of experiencing incident CI compared to younger women (2.02 95%CI(confidence interval) 1.37-2.97; p< .000) while age was not a statistically significant factor in the development of frailty. Higher education was associated with lower risk of CI (.57 95%CI .38-.86; p-value=.008). Higher number of comorbid conditions (3.11 95%CI .85, 11.42; p=.09) and obesity (2.24 95%CI .88-5.72; p=.09) were associated with experiencing increased risk of frailty, but this was not significant, and these were not associated with cognition. Taking three or four prescription medications compared to one or two was associated with lower risk of CI (.60 95%CI .37-.98; p=.042). The same comparison showed no significant alteration in risk of experiencing the co-occurrence of CI and frailty (3.45 95%CI .66-18.03; p=.14). Increased medication count also showed a positive trend for increased risk of frailty, but this association was not statistically significant.

Conclusion: In our study of healthy older women we did not find association between polypharmacy and incidence of CI and/or frailty. There is some evidence that polypharmacy is associated with an increased risk in the co-occurrence of CI and frailty and of frailty, but analysis on a larger population would need to validate this conclusion.

INTRODUCTION

The unique characteristics and health outcomes associated with older adults is becoming increasingly important as the population of individuals over the age of 65 continues to grow. By 2034, this population is expected to consist of 77 million individuals which, for the first time in history, will surpass the total population under age 18 (1). By 2060, this group is expected to make up over 23% of the total population of the United States (1).

COGNITIVE IMPAIRMENT AND FRAILTY

Cognitive impairment (CI) affects between 16% and 20% of older adults and is one of the most common geriatric conditions among adults aged 65 and older (2, 6-7). Frailty occurs in 10%-15% of community living older adults (8). Epidemiologic studies show that these two syndromes are frequently associated, and the association is bidirectional (7). Both conditions are considered to be part of decline processes involved in aging, and individuals over the age of 70 are at the greatest risk of experiencing these ailments (7).

Cognitive decline can be evaluated with neuropsychological tests which examine specific cognitive domains including executive function, psychomotor speed, and learning and memory (8-9). The Trail Making Tests assess psychomotor speed through an individual's ability to trace random numbers and letters in a set amount of time (9-10). The Hopkins Verbal Learning Tests use immediate and delayed recall measurements to assess learning and memory. Literature defines thresholds of impairment in any of these tests as at or below the 10^{th} percentile of performance, matched on age and education (9, 11).

Frailty is an individual's inability to respond to or resist stressors, either internal or external, which results from a decline in multiple physiological systems over time. Studies on frailty also discuss a decline in physiological reserves, or the capacity of the body to recover

from adverse events (12). Fried et al. has operationalized frailty as a syndromic phenotype that can be examined in geriatric studies (13). By her definition, individuals exhibiting at least three of the five characteristics related to phenotypic energetics are considered frail (13-14).

POLYPHARMACY

The all-inclusive definition of polypharmacy is broad: the concurrent use of multiple medications by an individual (3). More formal and specific definitions include number of medications such as five or more, duration of simultaneous medication use, or combination of unique drug ingredients (5, 15-16). The medication count definition of polypharmacy can be arbitrary and largely depends on the population of interest and the trends of medications over time (16-17). Consequently, there is a range of the prevalence of polypharmacy which relies on criteria of the applied definition. Regardless of definition, polypharmacy is becoming widespread in developed countries, especially among older adults as these individuals may be managing multiple chronic conditions with more than one prescription medication (16).

Globally, the amount of prescription medications dispensed has risen dramatically over the last 20 years. In a study on 300,000 individuals in Scotland, the average number of medications dispensed increased by 33% from 1995 to 2010 (3). In the United States, the prevalence of polypharmacy, defined as taking five or more medications, comparing data from 1999 to 2011 nearly doubled (15). As a result, polypharmacy as a concept holds importance as the aging population grows and as researchers continue to evaluate potentially inappropriate prescribing (PIP) (16).

In elderly populations, prevalence of polypharmacy ranges from 30% to 70%, and prevalence of PIP in older adults ranges from 12% in community-dwelling adults to 40% in adults living in nursing homes (18-19). Studies show that increasing age and increasing number

of chronic conditions contribute to increasing prevalence of polypharmacy (5). The relationship between polypharmacy and adverse health outcomes is largely driven by the risk associated with drug interactions in the case of multi-drug exposure (4-5, 18). The risk of adverse drug reactions increases as the number of medications taken increases and can be as high as 82% for those taking 7 or more medications (20). Adverse health outcomes associated with polypharmacy include emergency department visits, hospitalizations, hospital readmission, and mortality (5). In 1991, Beers criteria were established in order to increase awareness around potentially inappropriate medications and polypharmacy in the elderly population (21-22). These criteria have been revisited and revised, and pharmacological studies continue to look towards characterizing safe and unsafe polypharmacy exposures as the average number of prescription medications taken increases (16, 22).

Some studies have shown that polypharmacy can be associated with CI and frailty (23-24). In a study conducted by Niikawa et al. looking at community-dwelling adults >= 65 years of age, polypharmacy, which was defined as six or more prescribed medications, was two times more likely in cognitively impaired individuals when compared to those with normal cognition after adjusting for confounders (23). With respect to frailty, a study conducted by Saum et al. in Germany looked at community-dwelling adults aged 57-84 years of age and found that polypharmacy was associated with both prevalent and incident frailty for those taking five or more medications compared to those taking fewer than five medications (24). Understanding whether polypharmacy is associated with the risk of incident CI and frailty both separately and in combination can help inform issues associated with overprescribing in older populations.

METHODS

STUDY POPULATION

The WHAS II consists of 436 women aged between 70 and 80 years who were representative of the one-third least disabled women living in the community. Fried and Carlson detail the sampling and design of the study (9, 25). Exams took place every 1.5 years which included both physical, cognitive, and medication assessments with the exception between visit 3 and 4, when there were three years between visits. Of the 436 individuals followed in WHAS II, 433 had complete frailty measures and 395 had at least one complete cognitive test (9, 25).

Six participants with history of stroke and one with history of Parkinson's disease at baseline were removed because these conditions predispose individuals to CI and frailty. There were 87 individuals who were impaired in at least one of the four measures at baseline. They were removed from the analytic cohort as they had already experienced CI by our outcome definition and would not be considered at risk. Individuals who did not have first-round cognitive measures but had normal cognition in the second round were included as free of CI at baseline. Seven women were measured as frail at baseline and were removed from this analysis. Ten individuals did not have medication data at baseline and were removed. The combination of these exclusions for which some individuals fell into more than one category leaves a final analytic cohort of 284 individuals.

For the purposes of this analysis, six of the seven rounds of frailty measurements were used since there are only six rounds of cognitive measurements. Fifty participants reported use of antidepressants, antipsychotics, or Parkinson's medication at baseline. Models were run including and excluding these participants in order to assess the presence of confounding by indication.

EXAM MEASURES

Psychomotor speed and recall were evaluated using the Trail Making Test (TMT) Parts A and B and the Hopkins Verbal Learning Test (HVLT) which consists of immediate and delayed recall (10). The thresholds used to determine impaired cognition were determined as at or below the 10^{th} percentile of performance as defined in Reitan's studies of Trail Making Part A and B tests (10): TMT, Part A >= 81 seconds; TMT, Part B >= 225 seconds; HVLT immediate recall <= 16; HVLT delayed recall <= 4 (10, 26). Frailty was evaluated using the following five measures: weight loss, exhaustion, physical activity, walking speed, and grip strength. Individuals who met frailty criteria in three or more of these measures were considered frail (13-14).

Medication count was determined by unique medication information collected in-person by visual inspection at the baseline visit of the study. Each component medication within a drug was counted as a separate medication which is consistent with medication count measures (16). Supplements and over the counter medications, with the exception of aspirin, were removed from the count of medications per participant (16). Polypharmacy was assessed using categorical buckets. Four categories (no medications, 1-2 medications, 3-4 medications, five or more) were created based on the distribution of medication count in the data set along with supporting literature with respect to the definition of polypharmacy (3, 16, 21).

The following clinical and demographic measures were taken at baseline and included in this analysis: body mass index (BMI), number of chronic conditions, geriatric depression scale, education, and race. In addition to number of chronic conditions, we looked at diabetes mellitus, chronic obstructive pulmonary disease, cancer, osteoporosis, osteoarthritis, and spinal disc disease.

STATISTICAL ANALYSIS

Multivariable Cox proportional hazards models were used to evaluate how polypharmacy exposure influences all-cause mortality, incident CI, and incident frailty separately after accounting potential clinical and demographic correlates.

To understand hierarchical patterns of onset of CI and frailty, these outcomes were divided into the following four mutually exclusive groups: developed CI before frailty, developed frailty before CI, or developed both frailty and CI simultaneously. Mortality free of CI or frailty before the end of observation was the fourth competing outcome included in the analysis. The first instance in which an individual fell at or below at least one of the four cognitive tests was considered the onset of CI. These categorizations are consistent with Chu et al.'s paper which applied these criteria to National Health and Aging Trends data (2).

We used the Fine and Gray competing risks model to evaluate the risk associated with each of the four patterns of CI and frailty or mortality free of events with respect to exposure to polypharmacy (2, 27). Models adjusting for health correlates and demographic correlates were used to assess the independent relationships between prescription medication count and outcome patterns of CI and frailty.

In addition to polypharmacy, the final models include age, race, education, BMI, and number of comorbidities. We decided to treat age as a dichotomous variable comparing ages 70-75 to ages 76-80 at baseline after validating that similar results were produced when treating age continuously. Race was included in the model as binary to compare black participants to non-black participants. Education was also dichotomized to compare those completing at least high

school level education to those who did not complete high school after validating the negative association between education year completion and risk of CI (2, 28).

BMI categories were created with the World Health Organization's standardized buckets of underweight, normal, overweight, and obese (29). Only nine individuals were considered underweight and were recategorized to the normal weight category. Number of chronic diseases was bucketed into three categories by count of chronic diseases out of 14 possible conditions measured at baseline after looking at the distribution of disease count of the 284 participants. The following disease count categories were created: 0-1 diseases, 2-3 diseases, and 4 or more diseases. This analysis treats time as a continuous measure. All statistical analyses were conducted using Stata version 15.

RESULTS

BASELINE CHARACTERISTICS

Table 1 shows continuous and categorical measures of the medical and sociodemographic characteristics that were measured at baseline by polypharmacy category. The mean age of this sample was 73.8 years (SD 2.8). In this population, 108 (38%) had three or four comorbidities. Black individuals made up 33 (12%) of the population, and 228 (80%) had completed at least high school education. With respect to BMI, 111 (39%) were overweight and 56 (20%) were obese. In this initially healthy group, 58% had fewer than two comorbidities at baseline. The majority of this population (68%) had osteoarthritis at baseline, and 64 (23%) had chronic obstructive pulmonary disease (Table 1).

For the 284 participants, the overall mean prescription medication count was 3.2 (SD 2.5). Thirty-four (12%) individuals in this group had no exposure to prescription medications at baseline. Ninety-two (32%) took 1-2 medications, 86 (30%) took 3-4 medications, and 72 (25%)

took 5 or more medications. The 72 participants taking 5 or more medications at baseline had more comorbidities per individual than those taking fewer than 5 medications. Fifty-three percent of this group had at least two comorbidities compared to 30%-40% with two or more comorbidities for participants taking fewer than 5 medications. This group also had a larger proportion of participants with osteoporosis (17%) compared to an average proportion closer to 10% for the other medication exposure groups. Because of these differences in comorbidities for those taking 5 or more prescription medications, we decided to include polypharmacy as a categorical variable. This ensured our ability to investigate differences in risk of outcomes among participants taking 0, 1-2, and 3-4 medications (Table 1).

Table 1. Characteristics of WHAS II Analytic Cohort by Prescription Medication Count Category

	Total population (N=284)	No prescription medications (N=34)	1-2 prescription medications (N=92)	3-4 prescription medications (N=86)	5+ prescription medications (N=72)	P-value
Age 76-80, n (%)	76 (27%)	9 (26%)	22 (24%)	23 (27%)	22.0 (31%)	.82
Education High School or more, n (%)	228 (80%)	27 (79%)	82 (89%)	62 (72%)	57 (79%)	.041
Race – black, n (%)	33 (12%)	2 (6%)	9 (10%)	16 (19%)	6 (8%)	.10
BMI category						.63
Normal, n (%)	116 (41%)	18 (53%)	40 (44%)	32 (37%)	26 (36%)	--
Overweight, n (%)	111 (39%)	10 (29%)	36 (40%)	34 (40%)	31 (43%)	--
Obese, n (%)	56 (20%)	6 (18%)	15 (16%)	20 (23%)	15 (21%)	--
Geriatric Depression Scale ≥ 10, n (%)	14 (5%)	1 (3%)	2 (2%)	4 (5%)	7 (10%)	.15
Number of diseases category						.16
0-1 diseases, n (%)	164 (58%)	24 (71%)	56 (61%)	50 (58%)	34 (47%)	--
2-3 diseases, n (%)	108 (38%)	10 (29%)	34 (37%)	30 (35%)	34 (47%)	--
4 or more, n (%)	12 (4%)	0 (0%)	2 (2%)	6 (7%)	4 (6%)	--
Diabetes mellitus, n (%)	18 (6%)	0 (0%)	5 (4%)	10 (12%)	3 (4%)	.07
Chronic obstructive pulmonary disease, n (%)	64 (23%)	4 (12%)	18 (20%)	25 (29%)	17 (24%)	.18
Cancer, n (%)	25 (9%)	4 (12%)	7 (8%)	8 (9%)	6 (8%)	.9
Osteoporosis, n (%)	31 (11%)	4 (12%)	8 (9%)	7 (8%)	12 (17%)	.31
Osteoarthritis, n (%)	192 (68%)	22 (65%)	62 (67%)	58 (67%)	50 (69%)	.97
Spinal disc disease, n (%)	20 (7%)	2 (6%)	4 (4%)	6 (7%)	8 (11%)	.41
Taking antidepressants, n (%)	36 (13%)	0 (0%)	7 (8%)	13 (15%)	16 (22%)	.004

ALL-CAUSE MORTALITY

We first investigated the known and published associations between polypharmacy and all-cause mortality in light of literature focused on potentially inappropriate prescriptions (PIPs) and adverse drug events (ADEs) (17-19). We ran a multivariable Cox proportional hazards survival analysis controlling for clinical and demographic correlates. While the model output did not show a statistically significant relationship between increasing prescription medications and increased risk of mortality, the trend of association and inclusion of multimorbidity and BMI as correlates are consistent with literature (28, 30-31). Moreover, comparing those taking 1-2 medications to those taking 5 or more medications shows a risk of mortality that is 89% higher for those taking 5 or more medications after controlling for correlates in Table 2. Consequently, there is evidence of this relationship between increasing risk of all-cause mortality and polypharmacy for this population.

Multimorbidity of four or more diseases had a risk of mortality 3.62 (95%CI 1.40-9.35; p-value = .008) times the risk of mortality for those with fewer than two comorbid conditions (Table 2). Increasing age was also associated with all-cause mortality in a univariate model with evidence of association in this multivariable model (1.72 95%CI .97-3.05; p-value=.06). Literature supports this relationship, suggesting that our cohort is consistent with older populations sharing similar characteristics, and the lack of statistical significance is likely due to small sample size (30).

Table 2. Cox Proportional Hazards Model of all-cause mortality with polypharmacy, demographic, and clinical correlates

	Mortality (N=57)
Polypharmacy category	
0	Ref
1-2	.82 (.31, 2.20)
3-4	1.07 (.41, 2.80)
5 or more	1.57 (.62, 4.00)
Age	
70-75	Ref
76-80 years	1.72 (.97, 3.05)
Race	
Not black	Ref
Black	.89 (.33, 2.35)
Education	
Below High School	Ref
High School or more	.65 (.35, 1.20)
BMI	
Normal (18.5-24.9)	Ref
Overweight (25.0-29.9)	.72 (.40, 1.30)
Obese (30.0-34.9)	.74 (.33, 1.65)
Number of Diseases	
0-1	Ref
2-3	1.20 (.67, 2.13)
4 or more	3.62 (1.40, 9.35)*

* p-value < .05

COGNITIVE IMPAIRMENT AND FRAILTY

We also ran a multivariable Cox proportional hazards model for each outcome separately with the same variables as the all-cause mortality Cox model. There were 11 participants who experienced co-occurrence of CI and frailty. These participants were included in the Cox models as meeting criteria for both CI and frailty.

Out of the 284 individuals, 130 developed CI and 32 developed frailty. Polypharmacy was not significantly associated with increased risk of CI or frailty in either model (Table 3). Age was associated with increased risk of incident CI. Those ages 76 to 80 experienced a risk of CI 2.02 (95%CI 1.37-2.97; $p < .000$) times the risk for those ages 70 to 75. Education was also associated with occurrence of CI. Those with at least high school level education had a 43% (.57

95%CI .38-.86; p=.008) lower risk of CI compared to those who did not complete high school, controlling for BMI and comorbid conditions (Table 3).

In contrast to CI, neither age nor education were associated with incident frailty. Obesity (2.24 95%CI .88-5.72; p=.09) and four or more comorbidities (3.11 95%CI .85, 11.42; p=.09) show evidence of increased risk of frailty that is two to three times the risk of reference groups. While these associations were not statistically significant in these models, the trends show evidence of association which are consistent with existing literature (31-33) (Table 3). For the exposure of interest, polypharmacy, risk of developing frailty more than doubled (2.13 95%CI .59-7.74; p=.25) for those taking 3-4 medications compared to those taking no medications. Despite lack of statistical significance, this finding could be clinically meaningful.

Table 3: Cox Proportional Hazards Model for any cognitive impairment and any frailty with polypharmacy, demographic, and clinical correlates

	Outcome 1: CI (N=130)	Outcome 2: Frailty (N=32)
Polypharmacy category		
0	Ref	Ref
1-2	1.11 (.63, 1.99)	1.23 (.33, 4.61)
3-4	.82 (.45, 1.52)	2.13 (.59, 7.74)
5 or more	1.00 (.55, 1.85)	1.23 (.31, .4.92)
Age		
70-75	Ref	Ref
76-80	2.02 (1.37, 2.97)*	1.51 (.65, 3.50)
Race		
Not black	Ref	Ref
Black	1.48 (.87, 2.53)	.32 (.07, 1.50)
Education		
Below High School	Ref	Ref
High School or more	.57 (.38, .86)*	.93 (.36, 2.41)
BMI		
Normal (18.5-24.9)	Ref	Ref
Overweight (25.0-29.9)	1.04 (.70, 1.56)	.48 (.20, 1.15)
Obese (30.0-34.9)	1.43 (.86, 2.38)	2.25 (.88, 5.72)
Number of Diseases		
0-1	Ref	Ref
2-3	1.17 (.82, 1.69)	1.14 (.53, 2.44)
4 or more	1.36 (.53, 3.47)	3.11 (.85, 11.42)

* p-value < .05

PATTERNS OF ONSET OF COGNITIVE IMPAIRMENT AND FRAILTY

Evaluating patterns of CI and frailty requires accounting for competing outcomes and use of the Fine and Grey competing risks model (27). We assessed multiple competing risks models for each outcome of interest to estimate the subdistribution hazard ratios of CI first, frailty first, CI and frailty simultaneously, and mortality free of CI and frailty. Of the 284 individuals included in this analysis, 118 developed CI first, 21 developed frailty first, 11 developed both ailments simultaneously, and eight experienced mortality free of CI or frailty. The competing risks model for mortality free of CI or frailty failed to reach convergence because of the small sample size and was not included in these results.

Table 4. Competing Risk Model with polypharmacy, demographic, and clinical correlates of incident cognitive impairment and incident frailty

	Outcome 1: CI first Competing risks: frailty first, co-occurrence, death (N=119)	Outcome 2: Frailty first Competing risks: CI, co-occurrence, death (N=21)	Outcome 3: Co-occurrence, Competing risks: CI first, frailty first, death (N=11)
Polypharmacy category			
0	Ref	Ref	Ref
1-2	1.09 (.61, 1.97)	1.71 (.32, 9.13)	.61 (.05, 7.18)
3-4	.66 (.35, 1.25)	2.27 (.38, 13.58)	2.10 (.20, 22.03)
5 or more	.98 (.53, 1.84)	1.28 (.19, 8.60)	1.06 (.11, 9.91)
Age			
70-75	Ref	Ref	Ref
76-80 years	1.87 (1.28, 2.75)*	.94 (.31, 2.83)	1.74 (.43, 7.07)
Race			
Not black	Ref	Ref	Ref
Black	1.63 (.91, 2.92)	.17 (.02, 1.22)	.91 (.08, 10.16)
Education			
Below High School	Ref	Ref	Ref
High School or more	.54 (.36, .80)*	.84 (.25, 2.77)	3.11 (.33, 29.41)
BMI			
Normal (18.5-24.9)	Ref	Ref	Ref
Overweight (25.0-29.9)	1.17 (.77, 1.78)	.39 (.11, 1.18)	.75 (.19, 2.94)
Obese (30.0-34.9)	1.29 (.79, 2.13)	2.10 (.70, 6.34)	1.08 (.18, 6.47)
Number of Diseases			
0-1	Ref	Ref	Ref
2-3	.99 (.68, 1.44)	.47 (.14, 1.52)	3.81 (1.07, 13.53)*
4 or more	.88 (.33, 2.37)	2.38 (.40, 14.02)	4.28 (.36, 50.81)

* p-value < .05

Risk of developing CI first accounting for competing risks had similar statistically significant associations with age and education to the Cox model. Those 76 to 80 years of age were 1.87 (95%CI 1.28-2.75; p = .001) times more likely to develop CI first compared to those 70 to 75, and those with at least high school level education had a 46% (.54 95%CI .36-.80; p=.003) lower risk of developing CI first. These findings are consistent with studies conducted by Chu et al. and Gross (2, 26). Interestingly, in both the Cox model and the Fine and Gray model, the strong relationship between age and risk of CI persists even for this extremely narrow age range and small sample size. This suggests that age is a significant determinant of cognition in least disabled older women in their 70s. Race, BMI, and number of comorbidities were not associated with risk of developing CI first. The association between polypharmacy and having CI first for those taking 4 or fewer medications seems to be negative. When comparing participants taking 3-4 medications to those taking 1-2 medications, there was a 40% lower risk of developing CI (.60 95%CI .37-.98; p-value=.042) (Table 4).

For the 21 participants that experienced the outcome of frailty first, we again see similar results to the Cox model. Specifically, obese individuals have a higher magnitude of risk of developing frailty first when compared to those with normal weight (2.10 95%CI .70-6.34; p = .19) as do those with four or more comorbid conditions when compared to those with fewer than two comorbid conditions (2.38 95%CI .4-14.02; p = .34) (Table 4). While neither of these associations were statistically significant in this analytic sample, the magnitude of these figures along with supporting literature suggests evidence of this relationship in this population (31-33). Again, we see there was not an association between age and developing frailty first which indicates that beyond a certain number of years, age becomes less of a determinant in developing frailty first when looking at an older and narrower age range, a contrast to the strong association

between age and cognition. With respect to polypharmacy, we see a positive risk gradient as medication count increases from zero medications to 1-2 medications to 3-4medications. While not statistically significant, there might be clinical implications for this trend.

The 11 individuals experiencing a co-occurrence of CI and frailty had a higher average number of comorbid conditions compared to those experiencing a single ailment first. Every individual in this group had at least one comorbidity with eight of the 11 having three or more diseases at baseline. Participants with two or three diseases were 3.81 (95% 1.07-13.53; p = .039) times more likely to develop CI and frailty simultaneously compared to those with fewer than two diseases. There also seems to be a relationship between increasing age and increased risk of co-occurrence. This relationship resembles the association between increased age and the outcome of CI first. With respect to polypharmacy, the magnitude of the subdistribution hazard ratio comparing those taking three or four medications to those no medications is similar to the same comparison for the frailty first outcome (2.10 95%CI .20-22.03; p=.20) which provides some evidence that polypharmacy has a role in the onset of frailty, regardless of CI development.

VALIDATION

The proportional hazards assumption was validated for all Cox models using the Schoenfeld Residuals Test. Each model had p-values > .05 for this test indicating the proportional hazards assumption holds for this data set. We also validated the positive correlations between multimorbidity and polypharmacy which is consistent with literature on polypharmacy. Other correlations confirmed include the positive relationship between BMI and diabetes. Controlling for BMI was necessary as BMI contributes to an individual's absorption of medications (34).

SUB-ANALYSES

We ran all models in this analysis excluding number of comorbidities as a correlate. We did this in order to check for over adjustment as a result of the positive relationship between polypharmacy and number of diseases. Interestingly, excluding count of disease from these models did not change the Cox or competing risk hazard ratios. This suggests that polypharmacy may contribute to incidence of CI and frailty independent of number of comorbidities.

We also re-ran all models excluding individuals who were taking antidepressants which lowered the analytic population size to 248. There was little difference in the output of the models when this group was excluded, so we included these participants in order to increase statistical power of the models.

DISCUSSION

This longitudinal study with comprehensive clinical and demographic data and detailed follow-up improved our understanding of how certain characteristics contribute to risk and patterns of occurrence of two syndromes that come with aging: CI and frailty. For the 284 initially healthy women free of CI and frailty included in this analysis, there was evidence of multimorbidity and age being associated with all-cause mortality. With respect to CI, increasing age was strongly associated with increased risk of developing CI, and higher education was associated with lower risk of CI after controlling for demographic and clinical correlates. In the context of frailty, there was evidence that obesity and more comorbid conditions were associated with increased risk.

This analysis also shows some evidence of association between polypharmacy and outcomes of all-cause mortality, CI, and frailty. Our decision to treat polypharmacy as a categorical variable stems out of the different baseline characteristics exhibited in Table 1 for the

72 individuals taking 5 or more medications. Categorizing prescription medication count allowed us to investigate whether there was a risk gradient of polypharmacy with respect to each outcome of interest. There was a statistically significant and negative association in risk of CI comparing those taking 3-4 prescription medications to those taking 1-2 prescription medications. There was also evidence of association between taking 3-4 prescription medications and elevated risk of having frailty with or without co-occurrence of CI compared with those with 0 or 1-2 medications. The relationship between polypharmacy and outcome varied by pattern of onset of CI and frailty which builds upon the findings in Chu et al.'s studies regarding differential etiologic pathways for CI and frailty (2). Consequently, our analysis provides preliminary evidence that polypharmacy has a more detrimental effect on the development of frailty first or in conjunction with CI than for the onset of CI first.

Our findings largely agree with published studies regarding polypharmacy, CI, and frailty with respect to prevalence and risk associations. Distribution of prescription medication for this population and the proportion of individuals taking 5 or more medications (n=72, 25%) is consistent with the proportion of polypharmacy in other studies looking at people over age 65 (18, 21-23). The trend of association between increasing polypharmacy and all-cause mortality in our analysis is aligned with studies of polypharmacy and all-cause mortality in elderly populations in Berlin, France, and Brazil (28, 30-31). However, literature on the independent causal relationship between polypharmacy and all-cause mortality is mixed and relies on study population, the definition of polypharmacy thresholds, and control of confounding factors (35).

Our inconclusive results regarding polypharmacy and CI are also representative of ambiguous study results. Evidence of a positive association between polypharmacy and frailty is supported in studies on aging populations which show polypharmacy exposure can more than

double the risk of frailty (35). Our findings of statistically significant associations of age and education with CI are in line with previous findings published by Chu et al. on the National Health and Aging Trends Study and investigators of other longitudinal cohort studies (2, 28). The association between multimorbidity and frailty that we found is also consistent with the findings from Chu et al.'s analysis of the National Health and Aging Trends Study and systematic reviews of this positive association (2, 36). There are also studies which show evidence that obesity or unhealthy BMI is associated with frailty (37).

This study has a number of advantages: (1) its population-based design minimizes self-selection on outcomes of interest, (2) the study examined participants initially free of cognitive and functional impairment and followed them until they entered the target age-range for risk of CI and frailty, using a 11-year longitudinal design and (3) there were frequent and repeated comprehensive cognitive and physical assessments.

Limitations which should be mentioned in this analysis include (1) the treatment of polypharmacy as a fixed exposure at baseline, (2) the temporal measurement of CI and frailty outcomes which logs incidence at time of visit rather than the moment of occurrence between visits, and (3) the small sample size of those experiencing the outcomes which resulted in lower than desired statistical power. In addition, the thresholds for CI were extremely conservative which may dilute the relationship between more severe CI and polypharmacy. Conducting this analysis using dementia as the cognitive outcome of interest might provide clearer evidence of this relationship.

In summary, similar analyses should be conducted on a larger cohort with granular cognitive measurements, frailty evaluations, and pharmacological data. While there are several pharmacological data sets, few studies contain the same quality of assessment for frailty and CI

which was captured in the WHAS II, especially when looking at a population of healthy older adults. Studies with extensive measurements of cognition, frailty, and medication class would be extremely valuable in order to develop a deeper understanding of how polypharmacy affects the growing aging population.

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REFLECTION

My goals for this program and for this capstone project included developing expertise in the following competencies: Analytical/Assessment, Public Health Sciences, and Communication. This project not only allowed me to apply the analytical methods I had learned in the epidemiological and biostatistical methods series courses, but also challenged me to explore advanced statistical models beyond course materials. Mentoring from Qian-Li Xue, PhD and Sevil Yasar, MD, PhD exposed me to the academic and clinical application of this research in the gerontology field. My regular meetings with them allowed me to develop expertise in communication and interpretation of multivariable Cox Proportional Hazards models and competing risks models along with validation methods to ensure proper model application. In drafting the paper and uncovering relevant public health insights, I learned the nuance associated with communicating statistical findings. My advisors' mentorship was invaluable in my research and work on this topic as they provided context and perspective for statistical outputs that I may have overlooked as statistically insignificant. Ultimately, this project provided me with depth and clarity in the real-world application of the skills I have developed in the Epidemiologic and Biostatistical Methods Concentration.