


# Functional Status in Relation to Common Geriatric Syndromes and Sociodemographic Variables – A Step Forward Towards Healthy Aging

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**Purpose:** Geriatric syndromes (GS) are prevalent in the older population, with an impact on morbidity and disability. This study aimed to investigate the prevalence of functional dependence and ten GS in community older adults and to examine the different associations between these syndromes and sociodemographic variables and their impact on functional dependence.

**Patients and Methods:** A cross-sectional study of 342 outpatients seen at the geriatric clinic in the period 2015–2023.

**Results:** The mean age was 75±7.4. One-third had functional dependence and 96.2% had at least one GS. The mean number of GS was 3.11±1.74, ranging from 2.56±1.67 in the 60s to 3.55±1.70 in octogenarians. The most common GS found were polypharmacy (79.5%), musculoskeletal pain (49.7%), and Major Neurocognitive Disorder (MND) (32.7%). Polypharmacy was significantly associated with female sex and chronic pain, whereas sensory impairment was associated with male sex. MND, dizziness, and urinary incontinence were the only GS that significantly predicted functional dependence and were typically associated with increasing age.

**Conclusion:** Functional dependence increases as individuals age, paralleled by increases in MND, urinary incontinence, dizziness, sensory impairment, and constipation. Notably, only MND, incontinence, depression, and dizziness were significant predictors of functional dependence. Consequently, it is imperative to screen older adults presenting with these syndromes for early signs of functional decline to optimize their function and avert subsequent dependence, morbidity, and mortality.

**Keywords:** geriatric syndromes, functional dependence, elderly/older, ADL, Katz Index

## Introduction

The term “Geriatric Syndromes” (GS) is an umbrella for a group of multifactorial clinical conditions that do not fit into discrete disease entities and are highly prevalent in older adults, encompassing various non-specific symptoms and functional impairments. These syndromes often coexist and are associated with an increased risk of functional decline and frailty in the elderly population.<sup>1–4</sup> They include cognitive impairment, depression, falls, pain, urinary incontinence, dizziness, functional dependence and others.<sup>4</sup> Other less commonly studied syndromes include dizziness and pressure sores.<sup>4</sup>

Prevalence rates of GS have been widely variable; for example, high rates of “any” GS of 75% and 80% were found among community older adults in China and France, respectively<sup>5,6</sup> in contrast to relatively low rates of 49.9% in the USA.<sup>6</sup> Further lower rates of 16%, 19% and 22% of dementia, urinary incontinence and depression, respectively, were found in Thailand.<sup>7</sup> Moreover, polypharmacy,<sup>8,9</sup> falls,<sup>7,10</sup> sensory impairment,<sup>11</sup> chronic pain,<sup>12</sup> memory decline and depression<sup>6,11</sup> were also studied and found to be the most frequent GSs. This variability in the prevalence rates of “any” or “specific” geriatric syndromes is due to the lack of common ground and unified criteria for diagnosis and the inclusion of different sets of symptoms contributing to a syndrome.

Furthermore, some of these common geriatric conditions have been studied extensively, yet the specific impact and aggregate effect of those conditions on function and disability in the older adult population have not been investigated as thoroughly. The relationship between geriatric syndromes and functional decline/frailty is bidirectional and complex.<sup>1</sup> Firstly, geriatric syndromes such as falls, urinary incontinence, cognitive impairment, depression, and polypharmacy are known contributors to functional decline and frailty. These syndromes often lead to limitations in mobility, activities of daily living (ADLs), and social participation, thereby compromising overall functional status.<sup>1</sup>

Conversely, functional decline and frailty can exacerbate the development and progression of geriatric syndromes. As individuals become increasingly frail or functionally impaired, they may be more susceptible to falls, injuries, infections, and medication-related complications, further compromising their health and independence.<sup>2,4,6,13</sup>

Consequently, this study aimed to examine the prevalence of functional dependence and a selected set of ten presumably “common”<sup>1</sup> Geriatric Syndromes in community older adults and to examine the different associations between functional dependence, geriatric syndromes and sociodemographic variables, trying to fill the gap in this area of geriatrics research. It is hoped that this article will facilitate and enrich further studies on geriatric syndromes and help catalyze future research endeavors in this largely unexplored field.

## Methods

### Study Design and Participants

This cross-sectional study was carried out at the geriatric clinic affiliated with Jordan University Hospital and run by a consultant family physician with geriatric fellowship training during the years 2015–2023. Because all new referrals undergo a comprehensive geriatric assessment, data from the first visit, which was filled out by three trained medical interns in Excel sheets, was included. The geriatric clinic is a bi-weekly clinic accepting referrals from both the hospital and the community. Three to four new patients are seen in each clinic, totaling roughly 336 patients a year. Using OpenEpi, a total population of 2700 in 8 years was used, with a presumed frequency of the GS of 75% and a 95% confidence level yielding a sample size of 261.<sup>14</sup> A random number generator software was used to select the sample of new patients. Three hundred and forty-two new patients with complete data were included. Participants with missing or incomplete data were excluded.

### Demographic Features and Functional Dependence: Comprehensive Geriatric Assessment (CGA)

CGA data included medical history and sociodemographic information about living conditions and caregiving status, in addition to education and career history. Functional assessment utilized the Katz Index of basic activities of daily living (ADLs) ranging from 0 (totally dependent) to 6 (totally independent). Patients were considered functionally dependent when they had a dependence in at least one ADL, equivalent to a Katz Index of 5 or less.<sup>15</sup>

### Diagnosis of Geriatric Syndromes: Inclusion Criteria

Ten geriatric syndromes were selected based on data availability and the presence of literature showing they are common, associated with disability, and preventable.<sup>1</sup> Chronic constipation<sup>16</sup> and insomnia<sup>17</sup> were included because they are common yet understudied. The included syndromes are as follows:

#### **Cognitive Impairment (Major Neurocognitive disorder/ MND)**

Patients were considered to have MND if they had the criteria of MND as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition documented in their chart or if they were being treated for it.<sup>18</sup> House-bound patients and those with severe MND were excluded.

**Depression:** Patients were considered to have depressive symptoms if they scored  $\geq 5$  on the short form of the Geriatric Depression Scale or if they were being treated for depression.<sup>19</sup>

**Recurrent falls:** if they reported two or more falls in the past year.<sup>20</sup>

**Sensory impairment:** if participants self-reported at least one of the two deficits, if there was documentation about “trouble seeing” or “trouble hearing” affecting their daily living or if they were using a hearing aid.<sup>8,11</sup> Using reading glasses was not a criterion in this syndrome, nor were deafness and blindness.

**Polypharmacy:** being on five or more medications.<sup>21</sup>

**Musculoskeletal pain** was included if any of the following was present: patients subjectively complained of musculoskeletal pain involving one or more sites for most days of the week and was present for at least 3 months in the previous year, pain affecting the ability to perform ADLs, or pain needing regular pain killers.<sup>22</sup>

**Insomnia:** defined as a subjective complaint of difficulty falling or maintaining sleep, or nonrestorative sleep, producing significant daytime symptoms including difficulty concentrating and mood disturbances, according to the International Classification of Diseases-10 criteria<sup>17</sup> or if patients were taking sedatives or hypnotics.

**Dizziness** was recorded if patients subjectively complained of any form of dizziness and/or vertigo or were taking medications to treat them.<sup>23</sup>

**Chronic constipation** as a common geriatric syndrome is currently diagnosed with Rome IV criteria and the patient’s self-report.<sup>16</sup> That is, symptom onset should occur at least 6 months before diagnosis, and symptoms should be present during the last 3 months. More than one-fourth of defecation must include 2 or more of the following: straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction/blockage, manual maneuvers to facilitate defecations, and fewer than 3 spontaneous bowel movements per week.<sup>16</sup>

**Urinary incontinence (UI):** UI was defined as a self-reported presence of involuntary urine loss significant enough to require either pharmacologic or non-pharmacologic treatments.<sup>11</sup>

## Statistical Analysis

Data were transferred into SPSS version 22 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to describe sample characteristics and variables of the study including the mean number of geriatric syndromes and the Katz Index of Independence in ADLs.

The mean number of the geriatric syndromes was studied in relation to the dichotomous variables (sex, marital status and baseline function according to the Katz Index) using the independent *t*-test, and with the polychotomous variables (age strata, levels of education, job groups, caregiver status, and living arrangement) using the One-Way ANOVA test. When the results of the ANOVA test were significant, pairwise post-hoc comparisons were performed using the Bonferroni procedure. Results for  $P < 0.05$  were considered statistically significant.

A hierarchical multiple regression was run to determine if the addition of MND and then the rest of the studied geriatric syndromes improved the prediction of functional dependence over and above age and sex alone. The addition of MND to age and sex (confounding variables) in Model 2 led to a statistically significant increase in  $R^2$  of 0.073,  $F(1, 338) = 29.064$ ,  $p < 0.001$ . The addition of the rest of the GS to the prediction of functional dependence (Model 3) also led to a statistically significant increase in  $R^2$  of 0.192,  $F(9, 329) = 10.784$ ,  $p < 0.001$ . There was linearity as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin–Watson statistic of 1.781. All assumptions of homoscedasticity, multicollinearity, and normality were met. The full model was statistically significant,  $R^2 = 0.347$ ,  $F(12, 329) = 14.598$ ,  $p < 0.001$ ; adjusted  $R^2 = 0.324$ .

## Results

Data was completed for 342 participants. The baseline characteristics of the study sample are shown in Table 1. The mean age was  $75.5 \pm 7.4$ , including 62% females. Most of the participants were in their seventies (48%), married (67.5%), living with their partners or families, and primarily taking care of themselves.

Three hundred and twenty-nine patients (96.2%, 95% Confidence Interval (CI) 93.6%–98.0%) had at least one Geriatric Syndrome, and 33.3% (95% CI 28.4%–38.6%) were dependent in at least 1 ADL.

Post hoc Bonferroni test showed a statistically significant greater mean number of GS between the oldest and youngest age groups (mean number 3.55 vs 2.56, respectively.  $P = 0.001$ ), and between those with primary school education or less compared with those who had a high-school education ( $P = 0.034$ ). Further, living with a partner was

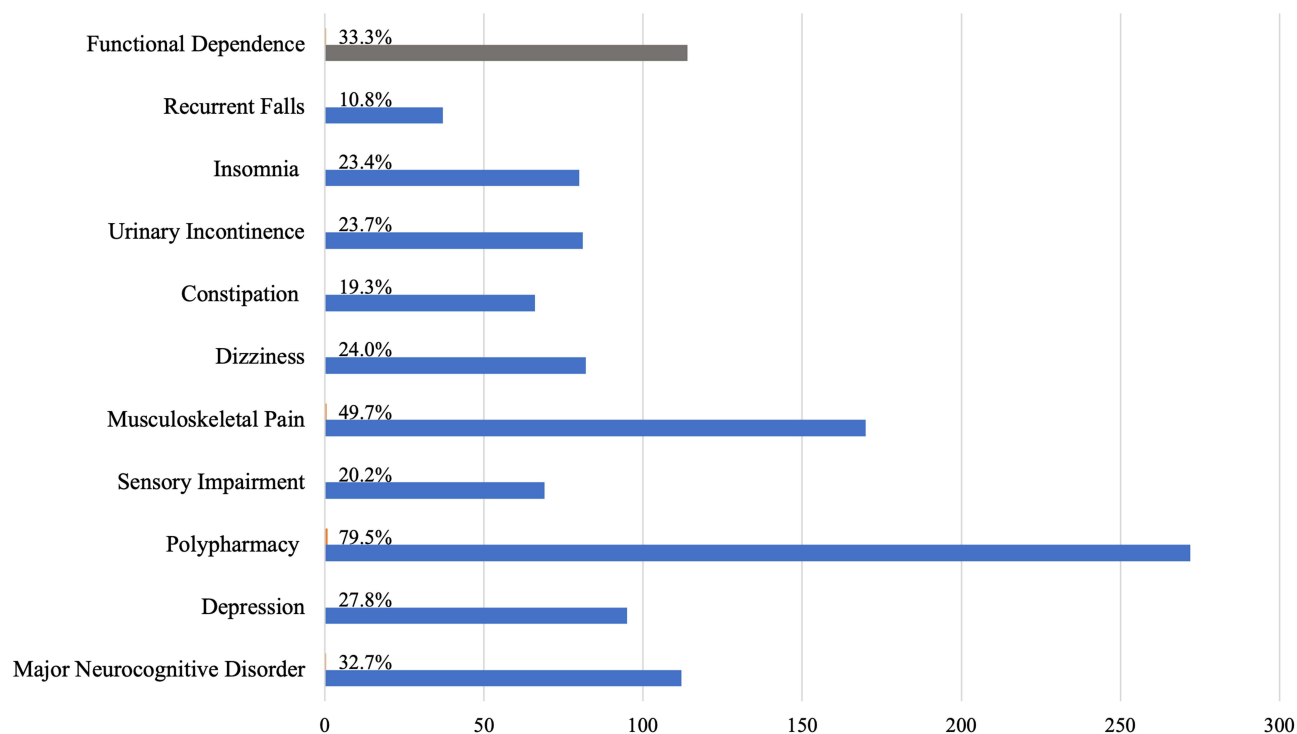
**Table 1** Descriptive Characteristics of the Study Population (N=342)

Demographic Variables	Number (%)	No. of Geriatric Syndromes <sup>a</sup> Mean± SD	P Value (ANOVA/t-Test)
<b>Mean No. of GS</b>		3.11±1.74	
<b>Age Groups</b>	Mean± SD	75.50±7.42	0.001
60–69	72 (21.1)	2.56±1.67	
70–79	164 (48.0)	3.07±1.67	
≥ 80	106 (31.0)	3.55±1.70	
<b>Sex</b>			0.728
Males	130 (38.0)	3.07±1.77	
Females	212 (62.0)	3.14±1.72	
<b>Marital Status</b>			<0.001
Unmarried	98 (28.7)	3.76±2.05	
Currently married	231 (67.5)	2.84±1.52	
<b>Education</b>			0.036
Primary School or less	186 (54.4)	3.31±1.71	
High School	80 (23.4)	2.73±1.55	
University Degree	76 (22.2)	3.03±1.94	
<b>Employment status</b>			0.195
Retiree	143 (41.8)	3.22±1.77	
Housewife	154 (45.0)	3.13±1.75	
Currently employed	45 (13.2)	2.69±1.56	
<b>Living</b>			<0.001
Alone	25 (7.3)	3.68±2.02	
With partner	133 (38.9)	2.59±1.44	
With family	184 (53.8)	3.41±1.81	
<b>Primary Caregiver</b>			<0.001
Self	215 (62.9)	2.64±1.53	
Partner	33 (9.6)	3.45±1.56	
Family	94 (27.5)	4.07±1.83	
<b>No. of Multimorbidities</b>			<0.001
0–1	30 (8.8)	2.43 ± 1.63	
2–4	216 (63.1)	2.94 ± 1.68	
≥ 5	96 (28.1)	3.70 ± 1.75	
<b>No. of Medications</b>			<0.001
0–4	70 (20.5)	1.93 ± 1.58	
5–9	172 (50.3)	3.28 ± 1.62	
≥ 10	100 (29.2)	3.64 ± 1.68	
<b>Baseline Function</b>	Mean Katz	5.12± 1.70	
Independent in ADLs (Katz Index =6)	228 (66.7)	2.66±1.61	<0.001
Dependent in ≥1 ADL (Katz Index ≤ 5)	114 (33.3)	4.02±1.635	

**Notes:** <sup>a</sup>Geriatric Syndromes include: Major Neurocognitive Disorder, depression, polypharmacy, sensory impairment, chronic musculoskeletal pain, dizziness, urinary incontinence, constipation, insomnia, and recurrent falls. Total number is 10 syndromes.

significantly associated with fewer geriatric syndromes compared to living alone ( $P=0.01$ ) or with a family ( $P<0.001$ ). Older adults who primarily take care of themselves had significantly fewer geriatric syndromes compared to those being taken care of by their family ( $P < 0.001$ ) or their partners ( $P = 0.02$ ).

Figure 1 shows that almost a third of the participants had functional dependence with a mean Katz Index of Independence in ADLs of five or less. Polypharmacy was the most prevalent GS, followed by chronic pain, major neurocognitive disorder (MND) and depression.



**Figure 1** Prevalence of Geriatric Syndromes and functional dependence among the study cohort.

**Table 2** shows the trend in the prevalence of the different GS and functional dependence among the three age strata for both sexes. Functional dependence, MND, sensory impairment, dizziness, urinary incontinence, and constipation were significantly associated with increasing age. Regarding the difference in the sex profile variable, polypharmacy was more prevalent in females ( $P=0.021$ ) whereas sensory impairment and dizziness were more prevalent in males ( $P=0.001$  and  $P=0.021$ , respectively).

**Table 2** The Prevalence of Geriatric Syndromes and Functional Dependence Among Age Strata

Geriatric Syndromes	Total N (%)	Age Group 60–69 N (%) <sup>a</sup>	Age Group 70–79 N (%)	Age Group +80 N (%) <sup>a</sup>	P value <sup>b</sup>
<b>Total</b>	342	72 (21.1)	164 (48.0)	106 (31.0)	
<b>MND</b>	112 (32.7)	14 (19.4)	50 (30.5)	48 (45.3)	<0.001
Males	47 (36.2)				0.293
Females	65 (30.7)				
<b>Depression</b>	95 (27.8)	18 (25.0)	48 (29.3)	29 (27.4)	0.793
Males	35 (26.9)				0.782
Females	60 (28.3)				
<b>Polypharmacy</b>	272 (79.5)	51 (70.8)	139 (84.8)	82 (77.4)	0.458
Males	95 (73.1)				0.021
Females	177 (83.5)				
<b>Sensory Impairment</b>	69 (20.2)	7 (9.7)	33 (20.1)	29 (27.4)	0.004
Males	38 (29.2)				0.001
Females	31 (14.6)				
<b>Musculoskeletal Pain</b>	170 (49.7)	39 (54.2)	82 (50.0)	49 (46.2)	0.297
Males	56 (43.1)				0.055
Females	114 (53.8)				
<b>Dizziness</b>	82 (24.0)	11 (15.3)	40 (24.4)	31 (29.2)	0.036
Males	40 (30.8)				0.021
Females	42 (19.8)				

(Continued)

**Table 2** (Continued).

Geriatric Syndromes	Total N (%)	Age Group 60–69 N (%) <sup>a</sup>	Age Group 70–79 N (%)	Age Group +80 N (%) <sup>a</sup>	P value <sup>b</sup>
<b>Constipation</b>	66 (19.3)	7 (9.7)	32 (19.5)	27 (25.5)	0.010
Males	20 (15.4)				0.151
Females	46 (21.7)				
<b>Urinary Incontinence</b>	81 (23.7)	12 (16.7)	36 (22.0)	33 (31.1)	0.021
Males	32 (24.6)				0.751
Females	49 (23.1)				
<b>Insomnia</b>	80 (23.4)	16 (22.2)	31 (18.9)	33 (31.1)	0.106
Males	24 (18.5)				0.092
Females	56 (26.4)				
<b>Recurrent Falls</b>	37 (10.8)	9 (12.5)	13 (7.9)	15 (14.2)	0.572
Males	12 (9.2)				0.459
Females	25 (11.8)				
<b>Functional Dependence</b>	114 (33.3)	12 (16.7)	47 (28.7)	55 (51.9)	<0.001
Males	43 (33.1)				0.937
Females	71 (33.5)				

**Notes:** <sup>a</sup>Percentages are within the age groups category. <sup>b</sup>P value of Mantel-Haenszel test of trend for age groups and Chi-Square test for sex groups.

**Table 3** Hierarchical Multiple Regression Model Predicting Functional Dependence from Geriatric Syndromes<sup>a</sup>

Geriatric Syndromes	B	t	95% Confidence Interval		P value
			Lower Limit	Upper Limit	
Constant	8.573	11.006			< 0.001
Age	-0.035	-3.339	-0.055	-0.014	0.001
Gender	0.024	0.159	-0.278	0.327	0.874
Major Neurocognitive Disorder	-0.535	-3.218	-0.862	-0.208	0.001
Depression	-0.345	-2.009	-0.683	-0.007	0.045
Polypharmacy	-0.178	-0.967	-0.540	0.184	0.334
Sensory Impairment	-0.191	-0.991	-0.570	0.188	0.323
Musculoskeletal Pain	0.024	0.162	-0.265	0.313	0.871
Dizziness	0.366	2.007	0.019	0.713	0.039
Constipation	-0.351	-1.868	-0.720	0.019	0.063
Urinary Incontinence	-1.337	-7.117	-1.706	-0.967	< 0.001
Insomnia	-0.293	-1.578	-0.659	0.072	0.116
Recurrent Falls	0.084	0.355	-0.381	0.548	0.723

**Notes:** <sup>a</sup>Age and gender were entered into Model 1, then Major Neurocognitive Disorder was added to Model 2 before the rest of the GS being added to the final model (Model 3).

Analyzing the predictive ability of each of the geriatric syndromes on functional dependence (Table 3) shows that MND, UI, depression, and dizziness were the only GS significantly predictive of functional dependence.

## Discussion

The cross-sectional study revealed a high prevalence of geriatric syndromes (GS) among participants, particularly polypharmacy, attributed to factors such as multimorbidities, chronic pain, and low education levels, with women showing significantly higher rates despite similar health conditions and lower education levels compared to men. Sex differences were also observed, with men more prone to sensory impairment and dizziness. Increasing age was associated with functional dependence, with certain GS such as dementia, depression, dizziness, and incontinence significantly predicting functional decline.

The high prevalence of the presence of any GS (96.2%) found in this study is not unexpected because the total number of included GS is high and the participants were recruited from a referral geriatric clinic where they undergo a comprehensive geriatric assessment (CGA); thus, the rate of detection of these syndromes is even higher and is believed to reflect the true prevalence.<sup>7,11</sup> Studies addressing the prevalence of GS show similar<sup>11</sup> to lower rates<sup>8,12,24</sup> probably because the total number of included GS is less and the likelihood of having at least one GS is subsequently less.

The most common GS seen in this study was polypharmacy. This could be related to the high prevalence of multimorbidities (91.2% had  $\geq 2$  multimorbidities) and chronic pain (50%) and the low levels of education (77.8% had high school and a lower level of education). Similar studies have shown that multimorbidities,<sup>25</sup> chronic pain,<sup>25,26</sup> and low educational attainment<sup>8–10,26</sup> were associated with more medications. It was also found that women significantly used more medications (polypharmacy) than men, despite the insignificant differences in multimorbidities or chronic pain. The significantly lower education level compared to men might explain this. Similar findings of sex differences in polypharmacy are also illustrated in the literature.<sup>27–29</sup> Further research is needed to understand the factors and predictors of polypharmacy in females.

On the other hand, men had significantly higher rates of sensory impairment and dizziness than women. Similar studies suggest that sensory impairment is a key factor in the multifactorial nature of dizziness in the older population.<sup>8,23</sup> Moreover, the use of prostate medications, especially alpha-blockers, is a recognized cause of orthostatic hypotension.<sup>30</sup> Additional research is required to examine the exact relationship between sensory impairment, dizziness and sex and their impact on functional status.

In line with the literature, this study revealed that aging predicted functional dependence with factors like socio-demographics, chronic diseases and co-occurring geriatric syndromes contributing to decline.<sup>4,8,13,31</sup> Likewise, the increment in the prevalence of some of the debilitating GS in this study (dementia (MND), UI, sensory impairment, and dizziness) with increasing age should not be overlooked as a culprit to aging-associated functional decline similar to other studies.<sup>4,6,9,11,32</sup>

Additionally, it is observed that the specific GSs that significantly predicted functional dependence included MND, depression, dizziness and incontinence. It is bewildering to try to explain functional decline based on presumed combinations of these four syndromes. Regardless, the exponential increases in both MND and urinary incontinence might explain the parallel increase in the prevalence of functional disability as the combination of “Dementia-Dependence-Incontinence” has been a well-studied dimension of clustered co-occurring syndromes.<sup>6,8,33</sup> The pathophysiological changes in the urinary tract coupled with the loss of inhibitory input on the detrusor muscles due to dementia, as well as a side effect of dementia treatment with cholinesterase inhibitors might explain the increased incidence of UI in dementia patients, especially with increasing age.<sup>34,35</sup> Other unstudied confounding variables might also play a role here although the direct relationship between UI and functional impairment is less well understood.<sup>36</sup>

Depression is another GS found to predict functional decline. Depression could be an isolated diagnosis or coexist with dementia and dizziness which in turn predict decline.<sup>1,37–39</sup> It is difficult, however, to establish any causal relationship between these syndromes due to the cross-sectional nature of this study. Either way, depression is a risk factor for functional decline and disability and vice versa and this dynamic long-term interdependence between them is crucial to supporting the view that regular screening for depressed mood and incipient functional decline may help to initiate early and appropriate interventions.<sup>40,41</sup>

Finally, dizziness was found to increase significantly with aging and to predict functional decline. It is suggested that dizziness is secondary to an age-related decline of acuity in the sensory and motor pathways within the central nervous system, in addition to environmental and pathological factors that include polypharmacy and depression.<sup>42,43</sup> Interestingly, dizziness was significantly associated with sensory impairment in this study; however, the high prevalence of polypharmacy might also be a contributing factor to dizziness. Whether dizziness was mainly related to polypharmacy,<sup>43</sup> depression<sup>37</sup> or other geriatric syndromes is a topic that needs further research because, as a geriatric syndrome, several factors might have caused dizziness, and resulted in functional decline in a direct or indirect way.<sup>23,37</sup> In any case, functional disability has been proven to be independently associated with dizziness.<sup>23</sup>

The major strength of this study is the relatively large sample size of community older adult patients who underwent a comprehensive geriatric assessment in an unbiased, out-of-study context. This strategy allowed us to study the



association between functional dependence and potential risk factors inherent to geriatric syndromes. Further, choosing a random sample is believed to add credibility and generalizability to the study results.

## Limitations

The study has several limitations that are worth mentioning. Firstly, its cross-sectional nature makes it inappropriate to draw cause-and-effect relationships. Secondly, relying on self-reported data is subject to recall and social-desirability biases and might be less accurate than using standardized tools. Although the sample was collected from one site, the clinic is located in the first University Hospital in the country and has patients attending from the whole kingdom.

## Conclusions

The present study is a preliminary effort to try to understand the prevalence and some of the complex relationships between selected geriatric syndromes including functional dependence. The results suggest an increased prevalence of some geriatric syndromes among community older adults, especially with increasing age. Polypharmacy, followed by chronic pain and Major Neurocognitive Disorder, were the most common geriatric syndromes. Polypharmacy was associated with female sex and chronic pain. Sensory impairment was more prevalent in males and was associated with dizziness. Increasing age and some geriatric syndromes such as MND, incontinence, depression and dizziness significantly predicted functional dependence.

In a nutshell, functional dependence is the geriatric syndrome that is considered a final common pathway of morbidity, disability, and other interacting geriatric syndromes. Studying the relationship between common geriatric syndromes and functional dependence is crucial to ensure healthy aging with the maximum functional potential.

It is believed that this research serves as a foundational framework for further development in the field of geriatric syndromes, in an effort to understand the complex interactions between the different syndromes and phenotypes. Further studies are still needed to assess which and how the geriatric syndromes and functional status are influencing each other in the older population, and the relationships between specific geriatric syndromes and multimorbidities.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon a reasonable request.

## Ethics Statements

This study was approved by the IRB committee at the University of Jordan (Number: 67/2019/650) and an informed consent was taken from all participants before enrolling their data in the study. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration.

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## Disclosure

The authors report no conflicts of interest in this work.

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