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RESEARCH PAPER

Depressive symptom heterogeneity among older adults after hip fracture

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Abstract

Objective: to evaluate patterns of depressive symptoms after hip fracture and examine their impact on functional recovery.
Methods: participants ($n = 304$) included older adults from the Baltimore Hip Studies 7th cohort who experienced a hip fracture. Depressive symptoms were measured at baseline or 2-, 6- or 12-month post-hip fracture using the 20-item Center for Epidemiologic Studies Depression scale. Gait speed was measured after hip fracture at 2-, 6- or 12-month follow-up. Latent class analysis was used to identify individuals with similar patterns of depressive symptoms after hip fracture. Item response probabilities characterised symptom profiles, and posterior probability estimates were used to assign participants to a baseline depressive symptom subtype. Weighted estimated equations compared post-fracture gait speed between baseline symptomatic and asymptomatic groups.
Results: four patterns of depressive symptoms were identified: asymptomatic (50.8%), somatic (28.6%), melancholic (11.4%) and anhedonic (9.2%). The somatic subtype was characterised by difficultly concentrating and reduced energy and movement, whereas anhedonic symptoms were associated with the inability to experience pleasure. Melancholic symptoms corresponded to anhedonia, decreased physical activity and other psychological and somatic complaints. Compared with the asymptomatic group, somatic symptoms were consistently associated with slower gait speed, −0.03 metres per second (m/s) and between-group differences for melancholic symptomology were as large as −0.05 m/s, but the associations were not statistically significant.
Conclusion: findings demonstrate unique depressive symptom subtypes in older adults after hip fracture and provide confirmatory evidence of unique clinical phenotypes; however, their impact on functional recovery after hip fracture remains unclear.

Keywords: hip fracture, depression, heterogeneity, physical performance, older people

Key Points

- Results highlight three unique symptomatic depressive symptom subtypes among older adults after hip fracture.
- First validation of similar previously identified clinical phenotypes using a quantitative data-driven approach.
- Personalised interventions targeted to unique depressive symptomology could improve depression screening and treatment outcomes.

Background

Hip fracture is a common, acute, musculoskeletal injury among older adults that is associated with psychiatric comorbidity [1, 2]. Specifically, depressive symptoms occur in up to 50% of patients immediately after hip fracture, often persist during recovery and may impede rehabilitation and contribute (in part) to why 50–75% of individuals experience permanent disability [3–5]. Prior studies have consistently demonstrated that depressive symptoms are associated with poorer clinical outcomes after hip fracture, including worse activities of daily living, mobility and other self-reported functional metrics [6–11]. Interventions for depression in affected hip fracture patients are needed to improve recovery; however, depressive symptoms are clinically and etiologically heterogenous and difficult to treat [12, 13]. Understanding different types of depressive symptoms that hip fracture patients experience could provide insight into what aspects of depression affect functional recovery and how to improve interventions that target both psychosocial and physical function [14].

Depression is routinely assessed as a single condition or severity continuum, which combines variegated symptomology together and reduces clinically relevant information critical for diagnosis and treatment [15]. Depressive symptom heterogeneity is characterised by non-specific symptomology, with variability in severity and trajectory, and numerous subtypes have been proposed but have limited clinical utility [12]. The 'Depression Symptomics' framework has been used to leverage data-driven methods to evaluate how patterns of depressive symptoms cluster and affect clinical outcomes [15, 16]. Additionally, evidence implies that older adults with musculoskeletal conditions experience unique constellations of depressive symptoms [17], but there is a lack of consistency and replication regarding subtype identification across studies, and confirmatory research is needed [16]. More importantly, no prior research has examined depressive symptom heterogeneity among older adults after hip fracture, and few studies have used objective functional measures when evaluating the relationship between depression and recovery of physical function [18, 19].

Identifying and validating depressive symptom subtypes among older adults with musculoskeletal conditions could lead to personalised interventions that target unique symptomatic profiles to improve clinical outcomes in patients with physical and mental morbidity [14]. Accordingly, the primary objective was to identify depressive symptom subtypes among older adults who experience a hip fracture. Given that hip fracture leads to difficulty walking, community ambulation has become a critical milestone during recovery and contemporary clinical trials have begun using walking ability as their primary outcome [20, 21]. Thus, a secondary study objective was to assess the influence of different depressive symptom subtypes on post-fracture gait speed.

Methods

Study sample

Participants were from the Baltimore Hip Studies 7th (BHS-7) cohort. The BHS-7 protocol was reviewed and approved by the University of Maryland Baltimore institutional review board (IRB) and participating hospitals' review boards; study methodology is available elsewhere [22]. Briefly, hospitalised adults over 65 years old or their proxies provided informed consent within 15 days post-admission for hip fracture. Exclusion criteria included: non-community dwelling prior to fracture, bedridden for 6 months prior to fracture, body weight >300 pounds, pathologic fracture, inability to speak English, residence >70 miles from hospitals, no surgery and contralateral hip hardware. Medical record review and anthropometric measurements were performed within 22 days of hospital admission for hip fracture. Interviewer-administered measures were collected at baseline and follow-up visits, whereas physical performance evaluations were only conducted at 2, 6 and 12 months after hip fracture.

A total of 362 participants (180 males and 182 females) consented to participate. Five participants did not provide data at either baseline or 2-month follow-up visits and another 18 participants were removed from the analysis sample as a result of an IRB-requested post-procedure audit (6 participants were subsequently found to be ineligible because they did not meet study inclusion criteria and 12 participants were determined to be ineligible secondary to failures in the informed consent process). BHS-7 participants ($n = 339$) were restricted to participants ($n = 304$) with at least one complete observation (i.e. no missing responses) for the 20-item Center for Epidemiologic Studies Depression (CES-D) scale, which included 279, 205, 151 and 150 participants at baseline and 2-, 6- and 12-month follow-up, respectively (Figure 1). The 279 participants with complete CES-D data at baseline were used in secondary longitudinal outcome analyses (Figure 2).

Depressive symptoms

The CES-D was measured at every time point and evaluates depressive symptoms occurring in the past week [23]. Item response options are presented on a four-point Likert scale, with scores ranging from zero to three, and higher ratings correspond to greater symptom frequency [23]. Positive items ($n = 4$) were reverse coded so that their interpretation was consistent with other items. Item scores were dichotomized to mimic classification of depression in the clinical setting using diagnostic criterion, an approach that has been used in prior studies [17, 24–26]. Scores of 2 or 3 were used to indicate the presence of a symptom, whereas scores of 0 or 1 corresponded to the lack of a given symptom. Dichotomous indicator variables were used to identify depressive symptom subtypes among BHS-7 participants during the year after hip fracture. Observations with missing responses were excluded.

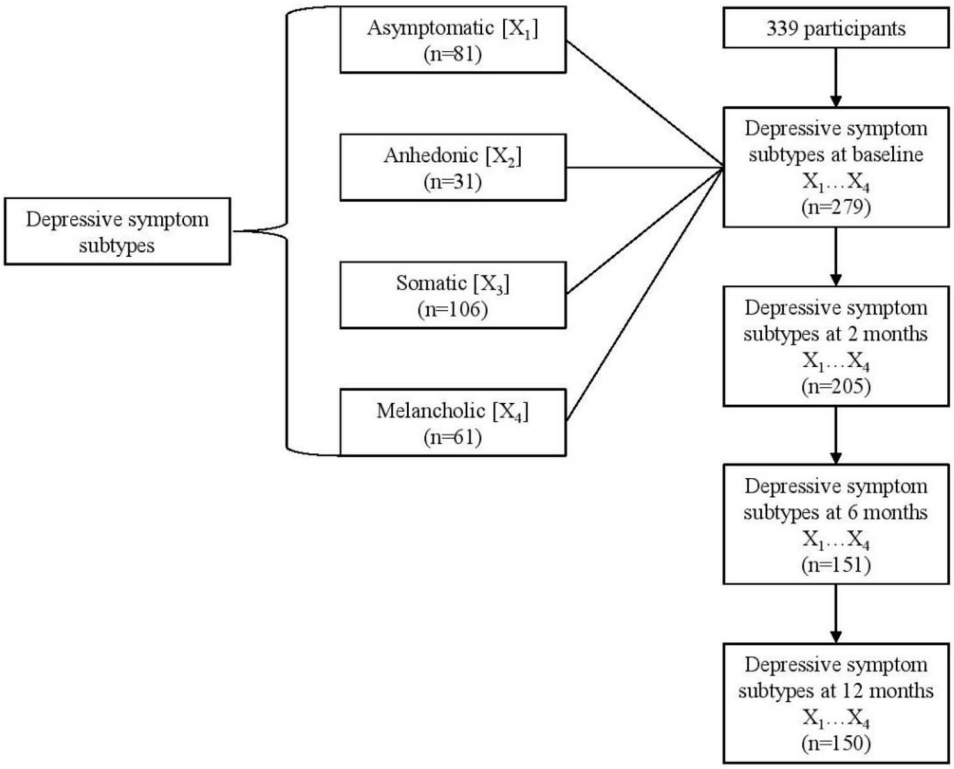

Figure 1. Study sample flow diagram for latent class analysis.

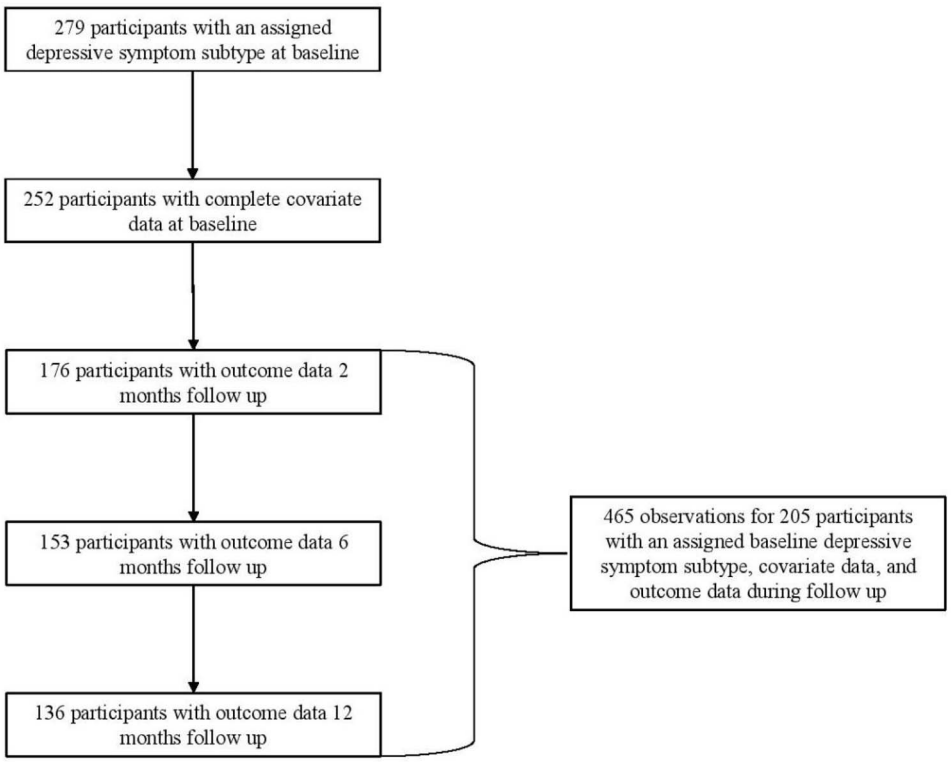

Figure 2. Study sample flow diagram for secondary longitudinal outcome analysis.

Gait speed

Gait speed assessments were conducted as part of Short Physical Performance Battery (SPPB) measurements on a 3-metre course, a walking speed distance that has shown similar test–retest reliability compared with longer lengths [27, 28]. Participants were instructed to stand with both feet together at the starting line, then to walk to the other end of the course 'at your usual speed, just as if you were walking down the street to go to the store', to keep walking through the end of the course, and to only stop after crossing the finish line [27, 28]. Participants were timed using a stopwatch, starting from when they began walking, and stopped once one of their feet completely crossed the finish line. Walking aids were allowed when endorsed by participant's attending physician; otherwise, they were encouraged to walk without assistive devices, and all participants wore a safety harness during testing. Small and medium effect-sized-based differences in gait speed correspond to differences of 0.03 metres per second (m/s) and 0.09 m/s, respectively [29].

Confounders

Potential confounders were selected *a priori* based on literature review. Comprehensive information was collected at baseline from medical records and self-reported measures, including age (years), sex, race (white or non-white), marital status (married, widowed, divorced, separated, never married), education (years), body mass index (kilogrammes per metres squared), physical activity, depression history, hip pain (yes or no), antidepressant use (never, past or current), resilience, social interaction, comorbidity and cognitive function. Physical activity was measured as hours per week using the Total Time Summary Index from the Yale Physical Activity Survey [30]. Hip pain was reported as 'pain in or around either hip joint, including the buttocks, groin, or either side of the upper thigh'. Pharmacological treatments for depression were assessed via a single question that asked about the use of antidepressants and referenced four specific medications: fluoxetine, sertraline, paroxetine and bupropion. Resilience was measured with a Resilience scale that was validated for the identification of older adults with low levels of psychological resilience [31]. Social interaction (number of social activities) was assessed using a modified social activity measure [32]. Comorbid conditions were evaluated with a modified version of the Charlson comorbidity index that omitted mild liver disease [33]. Cognitive function was measured with the modified mini-mental state examination (3MS) [34]. Depressive symptom severity was measured using the continuous CES-D score as well as the recommended CES-D screening threshold (CES-D score ≥ 16) for major depression [23].

Statistical analysis

Latent class analysis (LCA) is an approach that identifies subgroups based on multiple indicators of a given construct [35]. LCA models estimate the prevalence of mutually exclusive and exhaustive classes, item response probabilities in each group and posterior probabilities regarding the likelihood of membership to a given subtype [36]. Given the acute nature of hip fracture and to maximise available data, LCA models pooled all available CES-D observations and were implemented sequentially with one to five classes. Models were clustered by participants (N = 304) and fit using CES-D measurements ($n = 785$) from baseline ($n = 279$) and 2 ($n = 205$), 6 ($n = 151$), and 12 months ($n = 150$) follow-up. Measurement invariance concerning class prevalence and item response probabilities over time was evaluated; however, models did not achieve convergence when these parameters were unconstrained due to data sparsity; and therefore, were assumed to be constant during recovery. Akaike's information criteria (AIC) and Bayesian information criteria (BIC) fit statistics, class prevalence estimates and item response probabilities were used to identify and describe the optimal number of depressive symptom subtypes [37, 38]. Chi-square tests and analysis of variance assessed differences in baseline covariates between groups.

Most functional restoration occurs in the first 6 months after hip fracture, and the optimal point for intervention is immediately post fracture [3, 11]. Therefore, secondary analyses focused on the impact of baseline depressive symptom subtypes (assigned using posterior probabilities) on post-fracture gait speed. Weighted estimating equations (WEEs) that account for missing covariate and outcome data and selective survival modelled post-fracture gait speed by participants assigned baseline subtype [39]. WEEs were adjusted for potential confounders and included indicators for baseline subtypes, follow-up time and their interaction to evaluate between-group differences in gait speed after hip fracture. Marginal differences in gait speed by baseline depressive symptom subtype during the follow-up period were estimated with 95% confidence intervals (95% CI), and $\alpha = 0.05$ was used to define statistical significance. All analyses were conducted using Stata version 15 (Stata Corp, College Station, TX).

Results

Subtypes

A four-class solution was chosen based on fit statistics, prevalence estimates and clinical interpretability of the depressive symptom clusters. Identified subtypes (Table 1) after hip fracture included asymptomatic (50.8%), somatic (28.6%), anhedonic (9.2%) and melancholic (11.4%). Somatic symptoms were the most common at baseline (38.0%) but decreased in prevalence over time. Conversely, anhedonic symptoms (11.1%) were lowest in prevalence at baseline and remained stable during follow-up. Asymptomatic was the second most common group at baseline (29.0%) and increased in prevalence to 65.3% after 12 months. Similar to somatic symptoms, the prevalence of the melancholic subtype was the highest at baseline and decreased (21.9% to 5.3%) after hip fracture.

Table 1. CES-D item response probabilities in the original study sample (N = 304 participants, 785 person-visits)

CES-D items	Asymptomatic 50.8%	Somatic 28.6%	Anhedonic 9.2%	Melancholic 11.4%
1. I was bothered by things that do not usually bother me.	0.0982	0.3458	0.1629	0.6058
2. I did not feel like eating; my appetite was poor.	0.1271	0.4275	0.2955	0.7685
3. I felt that I could not shake off the blues even with help from my family and friends.	0.0076	0.1459	0.1130	0.8020
4. I felt that I was just as good as other people.[a]	0.1200	0.1083	0.3102	0.3626
5. I had trouble keeping my mind on what I was doing.	0.1001	0.3738	0.1676	0.6014
6. I felt depressed.	0.0055	0.2746	0.2429	0.8417
7. I felt that everything I did was an effort.	0.0927	0.5932	0.4176	0.8871
8. I felt hopeful about the future.[a]	0.1285	0.1648	0.6198	0.4364
9. I thought my life had been a failure.	0.0082	0.0370	0.1915	0.3633
10. I felt fearful.	0.0458	0.2104	0.0007	0.5618
11. My sleep was restless.	0.2407	0.5258	0.4461	0.7104
12. I was happy.[a]	0.0395	0.1223	0.8965	0.5368
13. I talked less than usual.	0.0997	0.2590	0.2551	0.3867
14. I felt lonely.	0.0693	0.2570	0.2441	0.7352
15. People were unfriendly.	0.0174	0.0699	0.0541	0.3394
16. I enjoyed life.[a]	0.0487	0.2057	0.6496	0.5413
17. I had crying spells.	0.0000	0.0402	0.0283	0.2669
18. I felt sad.	0.0153	0.2294	0.1194	0.7321
19. I felt that people disliked me.	0.0146	0.0295	0.0173	0.2483
20. I could not get 'going'.	0.0371	0.3464	0.2225	0.6161

AIC: 12,724.23; BIC: 13,106.816. [a]CES-D item reverse scored and coded.

Depressive symptom severity was highest in the melancholic subtype, comparable between the anhedonic and somatic groups, and lowest among asymptomatic participants. The proportion of individuals satisfying CES-D screening criteria immediately after hip fracture was 1.2% for asymptomatic participants, 58.1% for anhedonic participants, 62.3% for somatic participants and 100% for melancholic participants. Asymptomatic was characterised by uniformly low item response probabilities for all depressive symptoms. Somatic symptoms included reduced energy and movement, impaired concentration and other related complaints (e.g. restless sleep). Anhedonic symptoms were distinguished by the inability to feel happiness and hopelessness. The melancholic subtype had the largest number of depressive symptoms, including depressed mood, sadness, loneliness, decreased energy and movement and other physical problems.

Subtype characteristics

Participants classified as asymptomatic, somatic or melancholic were more likely to be female, whereas anhedonic symptoms were associated with being male (Table 2). Socioeconomic status as measured by years of education was higher in the asymptomatic and anhedonic subtypes compared with the somatic and melancholic groups. Somatic symptoms were associated with the highest level of pre-fracture physical activity and the lowest likelihood of prior depression. Conversely, pre-fracture physical activity was lowest in those with anhedonic symptoms, and the melancholic group had the highest proportion of individuals with prior depression. Also, psychosocial health as measured by social interaction and resilience was lower among those with anhedonic and melancholic symptoms compared with participants in the somatic and asymptomatic groups. Comorbidity was comparable between the asymptomatic, somatic and anhedonic subtypes but higher among participants with melancholic symptoms.

Gait speed recovery

Multivariable adjusted estimates of between-group differences in gait speed (Table 3) generally showed slower walking ability among participants in symptomatic depressive subtypes, but none of the associations were statistically significant ($P \geq 0.05$). For example, participants with somatic symptoms were consistently estimated to have slower average gait speed (~ -0.03 m/s) from 2 to 12 months post-fracture: -0.035 m/s (95% CI: -0.129, 0.060; $P = 0.474$) and -0.030 (95% CI: -0.124, 0.065; $P = 0.536$), respectively. Similarly, marginal effect estimates for melancholic symptoms suggested slower gait speed at 6-months follow-up (B = -0.054; 95% CI: -0.170, 0.060; $P = 0.352$) and 12 (B = -0.030; 95% CI: -0.140, 0.081; $P = 0.597$). Associations for anhedonic symptoms varied and showed no consistent magnitude or direction.

Discussion

Results contribute to literature on depressive symptom heterogeneity and highlight four subtypes among older adults with hip fracture. Half of participants reported depressive symptoms after hip fracture that were comprised of three active subtypes, a proportion that is consistent with symptomatic clusters identified in large population-based samples of older adults [40]. Furthermore, constellations of

Table 2. Participant characteristics by baseline depressive symptom subtype in the secondary analysis sample[a]

	Asymptomatic		Somatic		Anhedonic		Melancholic		*P*
Variable, m (SD) or *n* (%)	*n* = 81		*n* = 106		*n* = 31		*n* = 61		
Age (years)	79.8	(7.7)	80.1	(7.7)	82.0	(6.7)	80.9	(8.0)	0.539
Female	48	(59.3%)	54	(50.9%)	9	(29.0%)	33	(54.1%)	0.039
White	70	(87.5%)	99	(95.2%)	30	(96.8%)	57	(93.4%)	0.172
Marital status									0.347
Married	36	(44.4%)	44	(41.5%)	13	(41.9%)	24	(39.3%)	
Widowed	36	(44.4%)	45	(42.5%)	15	(48.4%)	24	(39.3%)	
Divorced	6	(7.4%)	8	(7.6%)	1	(3.2%)	6	(9.8%)	
Separated	–	–	1	(0.9%)	–	–	4	(6.6%)	
Never married	3	(3.7%)	8	(7.6%)	2	(6.5%)	3	(7.9%)	
Education (years)	13.6	(3.1)	12.8	3.6	14.6	(3.1)	12.8	(3.4)	0.031
Hip pain	8	(10.1%)	22	(22.0%)	3	(10.7%)	8	(14.0%)	0.136
Physical activity (hours/week)	15.6	(12.6)	20.1	14.1	12.2	(10.5)	13.1	(12.1)	0.002
Depression history	15	(18.5%)	15	(14.2%)	7	(22.6%)	22	(36.1%)	0.009
Antidepressant use									0.080
Never	61	(75.3%)	72	(69.2%)	22	(71.0%)	34	(56.7%)	
Past	1	(1.2%)	8	(7.7%)	–	–	6	(10.0%)	
Current	19	(23.5%)	24	(23.1%)	9	(29.0%)	20	(33.3%)	
BMI (kg/m^2)	25.0	(5.7)	26.1	(5.7)	24.9	(3.9)	24.5	(3.9)	0.218
Resilience	6.0	(0.8)	5.8	(0.8)	5.2	(0.7)	5.1	(0.9)	<0.001
Social interaction	12.5	(9.4)	11.3	(9.7)	10.7	(8.4)	7.7	(8.3)	0.025
Charlson comorbidity	1.7	(1.7)	1.9	(1.8)	1.9	(1.6)	2.5	(1.9)	0.045
3MS	89.6	(10.5)	86.1	(13.9)	84.4	(12.5)	85.3	(12.7)	0.102
CES-D	6.9	(3.8)	17.0	(5.4)	18.0	(6.5)	33.1	(7.5)	<0.001
CES-D ≥ 16	1	(1.2%)	66	(62.3%)	18	(58.1%)	61	(100.0%)	<0.001

BMI: body mass index; M: MeanSD: standard deviation. [a]Descriptive statistics were estimated using all available participants and data among those with an assigned baseline depressive symptom subtype and may contain missing information.

Table 3. Adjusted time-specific differences in gait speed after hip fracture comparing symptomatic to asymptomatic baseline depressive subtypes

Time point	Somatic			Anhedonic			Melancholic		
	B	(95% CI)	*P*	B	(95% CI)	*P*	B	(95% CI)	*P*
2	−0.034	(−0.129, 0.060)	0.474	0.055	(−0.071, 0.180)	0.391	0.002	(−0.105, 0.109)	0.968
6	−0.030	(−0.124, 0.064)	0.533	−0.017	(−0.157, 0.123)	0.807	−0.054	(−0.170, 0.060)	0.352
12	−0.030	(−0.124, 0.065)	0.536	0.005	(−0.129, 0.138)	0.945	−0.030	(−0.140, 0.081)	0.597

B: Beta coefficient. Baseline confounders: age, sex, race, marital status, education, physical activity, body mass index, comorbidity, depression history, antidepressant use, hip pain, social interaction, resilience and cognitive function.

depressive symptoms from the three active subtypes and their overall prevalence (∼50%) are congruent with phenotypes described among participants enrolled in the Osteoarthritis Initiative [17]. Among symptomatic subtypes, findings suggested that somatic and melancholic symptoms resulted in clinically slower post-fracture gait speed, but there was wide variability associated with effect estimates. Nonetheless, results illustrate distinct patterns of depressive symptoms that represent differences in both clinical presentation and severity.

Few studies have evaluated depressive symptom heterogeneity among older adults with musculoskeletal conditions, surprising, considering the high prevalence and detrimental effects [16, 18, 41–43]. Anhedonic symptoms characterised by the inability to experience pleasure (i.e. low positive affect) were the least common after hip fracture. Prior research implies that anhedonic subtypes are rarely reported, and depressive symptoms in general population older adults are differentiated by negative affect and somatic symptoms [16, 40]. In contrast, somatic symptoms typified by difficulty concentrating and decreased energy and movement were the most prevalent. Depressive symptom subtypes with similar clinical presentations that lack cardinal symptoms of depression (i.e. low mood and anhedonia) have been more broadly identified among healthy older adults, individuals with or at-risk for knee osteoarthritis and cancer patients [17, 40, 44, 45]. Given that depressive symptoms in general population older adults are characterised by somatic complaints and negative affect, the scarcity of anhedonic subtypes reported in previous studies suggests low positive affect could be symptomology that presents at the interface of ageing and functional disability [16, 17, 40]. Moreover, it is unclear whether individuals with somatic complaints related to symptoms of depression are indicative of other

medical conditions (e.g. delirium, frailty, etc.). Melancholic symptoms were distinguished by the widest symptomology spectrum and are the most consistently identified subtype [16]. The co-occurrence of distinct symptom clusters may represent differentiation through higher severity rather than unique symptomatic expression. Reproducibility has been an issue regarding data-driven assessments of depressive symptom heterogeneity, and these findings provide the first validation of similar experimental phenotypes identified in a study among persons experiencing pain and functional disability [16, 17, 46].

Results regarding depressive symptom subtypes and gait speed after hip fracture and their clinical implications are unclear. Prior research uniformly implies that depression is associated with worse post-fracture functional recovery [6–11]. The magnitude of the associations for somatic and melancholic groups compared with asymptomatic participants ranged from −0.03 to −0.05 m/s, which are suggestive of clinically meaningful differences in post-fracture walking ability [29]. However, there was very little measurement precision associated with these effect estimates, and depressive symptoms as operationalised in this study may have little or no impact on clinical outcomes after hip fracture. Thus, findings from the current and prior studies may indicate that depression severity and not subtypes affect post-fracture functional recovery. This contention is supported by a study demonstrating that post-fracture depressive symptoms satisfying CES-D screening criteria for major depression are associated with clinically slower improvement in SPPB score [18]. Nonetheless, previous research indicates that slower gait speed as low as 0.009 m/s predicts greater mortality [47]. Therefore, even small effects on walking ability that differ by depressive symptom subtype are potentially clinically relevant during hip fracture recovery. This assertion is consistent with previous data showing that older adults with non-dysphoric (i.e. without sadness) and melancholic depressive symptoms experience greater functional disability [17, 48]. Moreover, if somatic and melancholic depressive symptoms persisted after hip fracture, then any detrimental effects on functional recovery could also increase in magnitude [19]. Accordingly, results motivate future research using other patient populations, larger samples and more sophisticated study designs that could firmly establish the potential clinical importance of the nascent data presented in this report.

This study's limitations warrant consideration. First, depressive symptoms were measured using the CES-D, which was not developed to reflect diagnostic criteria for depression, and it does not assess all symptoms (e.g. atypical) associated with major depressive disorder [23]. The 7th item on the CES-D has also been shown to inflate case ascertainment among older adults or those with painful conditions (i.e. hip fracture) [49]. Similarly, there is potential for overlap between depressive symptoms and other medical conditions associated with ageing, where the measurement model could detect symptomology of both conditions and not a unique subtype. Third, a three-step LCA implementation with exposure uncertainty was used, but any misclassification bias would attenuate outcome associations to the null [36]. The current study design also defines latent states (classes) at a single snapshot in time and provides no information on how unobserved group trajectories progress over time. That said, the motivation was to identify modifiable depressive symptom subtypes with the potential for informing hip fracture interventions when information on longitudinal depressive symptomology is not available to clinicians. Lastly, there is always potential for residual and/or unmeasured confounding of the exposure-outcome relationship in any observational study.

To summarise, this research represents the first confirmatory study of depressive symptom subtypes among older adults with musculoskeletal disorders. Results imply that 50% of older adults have moderate-to-severe depressive symptoms after hip fracture that cluster into three distinct phenotypes; however, their impact on walking ability during hip fracture recovery remains unclear. To fully understand the meaning and implications of our findings, further confirmatory research is necessary and studies evaluating how unobserved group trajectories progress over time. If data-driven methods can consistently identify depressive symptom subtypes across musculoskeletal conditions and depression measures, it may be possible to develop algorithms to improve depression screening and treatment procedures.

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