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Pictures of sculptures by Gustav Vigeland, taken by B. Ritz, at the Vigeland Park, Oslo, Norway, illustrating sleep and disturbances in the elderly.

# Parkinson's Disease Motor and Non-Motor Features Accompanying Insomnia and Excessive Daytime Sleepiness Symptoms, a Large Population-Based Study

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Research Article

# What Makes Us Walk: Predictors and the Interplay of Physical and Cognitive Factors on Gait Speed in Community Dwelling Older Adults

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**Abstract**

This study investigated the predictors of gait speed in community dwelling older adults while examining interplay between physical performance and cognition on comfortable and fast gait speed. Sixty-six community-dwelling older adults (mean age 80.8 71% female) completed the following: 30-Second Chair Stand (30-SCS), Functional Reach (FR), Flanker Task, Digit Symbol Substitution Test (DSST), and gait speed (comfortable and fast). Hierarchical linear regression examined the relationship of comfortable and fast gait speeds with physical performance (30-SCS, FR) and cognitive domains (DSST, CDT, Flanker effect). Unique predictors of comfortable gait speed included 30-SCS (B=1.86, p<0.001), FR (B=3.37, p=0.005), and Flanker effect (B=-0.02, p=0.05). Unique predictors of fast gait speed included 30-SCS (B=2.61, p<0.001), FR (B=3.58, p=0.04), and DSST (B=0.95, p=0.01). Both comfortable and fast gait speed were primarily predicted by strength and balance while cognitive factors, including executive function and processing speed, also contribute to predicting gait speed. Lower extremity strength and balance are independently predictive of both comfortable and fast gait speed. Executive function and cognitive inhibition, as assessed by the Flanker effect, predicted comfortable gait speed, while processing speed, as assessed by the DSST,

predicted fast gait speed. These results corroborate previous literature that examined functional and cognitive domains individually.

**Keywords**
Functional outcomes; gait speed; rehabilitation; cognition

## 1. Introduction

Adults aged sixty or older numbered an estimated 962 million worldwide in 2017, with the expectation that this number will double by 2050 [1]. In the United States alone, adults aged 65 and or older comprised 15.2% of the population in 2016, numbering 49.2 million [2]. To optimize health and function in this growing population, clinicians and researchers alike must understand the most influential factors on future health and wellness. Additionally, it is important to determine inexpensive and efficient outcomes measures that can identify decline in those factors which are amenable to intervention. Gait speed is one such factor that is both easily measurable and has established reliability and minimum detectable change values [3, 4]. These strong psychometric properties and versatile clinical utility have contributed to gait speed being considered "the 6th vital sign" [5]. It is recognized as a valid tool that has demonstrated predictive ability for both functional mobility and overall health status [3]. Gait speed has been identified as a key indicator in other important health outcomes, such as mortality, institutionalization, and dependence in daily activities; therefore, it crucial to understand the factors that may influence an older adults' gait speed [5].

Mobility through ambulation is required for independence with activities of daily living and participation in community activities. Further, older adults must be able to vary their gait speed to successfully and safely complete functional tasks such as hurrying to the rest room or crossing a busy street. In a healthy population of older adults, those individuals ambulating at a speed below a cut off of 1.0 meters per second have been found to be at higher risk for health related outcomes including lower extremity limitations, hospitalization, and death [6]. Faster gait speeds overall have been found to be associated with higher levels of independence and survival in older adults [7, 8]. Both comfortable and fast gait speeds have demonstrated prognostic value for identifying health related outcomes such as disability [9, 10], falls [11, 12], cognitive decline [13], and mortality [11].

Current literature recognizes a number of influencing variables on gait speed including balance [14-17], lower extremity muscle strength [14, 15, 18, 19], cognition [20-22], and demographic characteristics (e.g. age) [17]. In particular, age related decreases in strength have a substantial impact on physical performance including gait speed. With primary aging, type II muscle fibers decrease with an additional reduction in motor unit innervation [23]. Lean muscle mass decreases as fat mass increases resulting in sarcopenia [24]. As a result, there is an overall reduction in muscle strength, leading to potential functional mobility limitations and a higher risk for falls and hospitalizations [25]. Multiple studies have identified both composite lower extremity muscle strength and individual muscle strength as predictive variables for comfortable and fast gait speeds [14, 18, 26-28]. Aranda-Garcia (2015) found that isometric knee extensor strength was the

best predictor of fast gait speed in community dwelling older adults, explaining 47.5% of the variance in both global characteristics and physical abilities models. Similarly, another study reported that isometric knee extensor strength explained 36% of the variance of comfortable gait speed among a sample of 839 older adults [18]. Balance has also been shown to influence gait speed through assessment of various components of standing balance [14-17].

Another variable to consider during evaluation of the older adult is cognitive function and its impact on physical abilities. Gait requires cognitive integration of motor commands and perceptual sensory inputs to execute a normal gait cycle [29]. Daily life often requires older adults to adapt to environmental demands while walking and, under these circumstances, cognitive resources are in higher demand [29]. Callisaya and colleagues (2017) found that older adults with higher levels of cognitive impairment had slower comfortable and fast gait speeds and poorer ability to increase gait speed. Determining the most important cognitive domains related to gait speed is essential to development of cognitive interventions for mobility decline and disability. Domains of executive function and processing speed have been associated with gait parameters, including gait speed [20-22, 30, 31]. Executive function includes multiple processes including attention, planning, organizing, inhibition, and directing goal-oriented behavior. Processing speed is the time to perceive, process, and direct cognitive information. Martin et al. (2012) found that executive function and processing speed were independently associated with comfortable gait speed along with other associated gait parameters. Another study found that measures of executive function, processing speed, memory, and verbal IQ explained 16% of the variance of comfortable gait speed among 186 community-dwelling older adults [32]. Further, it has been reported that a faster reaction time is associated with increased comfortable gait speed with the authors postulating that a slower reaction time may be related to reduced central processing speed [17] To add to these findings, numerous longitudinal studies have reported that lower baseline scores on tests of executive function, processing speed, and memory led to faster yearly decline in walking speed [30, 33, 34]. Although these relationships are strong, few studies have included other measures of physical function in their analyses to determine if there is shared variance between cognitive and physical variables.

The current literature offers some insight into the role of physical and cognitive factors on predicting gait speed, however a gap in the literature is present in regard to the interplay between these factors. Very few studies include both physical performance and cognitive measures in the same analyses. Understanding if shared variance exists between strength, balance, and specific cognitive domains can guide clinical treatment when gait speed deficits are present. Further, many studies investigating the influence of cognition have focused on comfortable gait speed, but not fast gait speed. It is important to determine if both comfortable and fast gait speed are influenced by the same factors or if they should be considered separately during the evaluation and treatment of older adults as prior studies have found differences in predictor variables (Mantel et al., 2018). Therefore, the aim of the current study was to investigate the unique predictors of both comfortable and fast gait speed in community dwelling older adults using measures of cognition and physical performance. Two hypotheses were made: 1) lower extremity strength and balance would be strong predictors of both comfortable and fast gait speed with statistical control of cognitive variables and (2) executive function would be the strongest cognitive predictor of both comfortable and fast gait speed.

## 2. Methods

### *2.1 Participants and Study Design*

Participants included 66 community-dwelling older adults recruited from two retirement communities in Florida. A sample size of 66 was determined based on a power of 0.80, an alpha level of ≤ 0.05 with a medium to large effect size as demonstrated by previous literature regarding the predictors of gait speed, and use of four to six independent variables in a multiple linear regression model [35]. Participants were initially screened through a telephone interview to determine eligibility based on the following inclusion criteria: 60 years of age or older and able to walk at least 20 feet without an assistive device. Participants provided verbal informed consent prior to participation.

### *2.2 Procedure*

This observational study was composed of a one-time data collection scheduled individually for each participant. Upon receiving verbal informed consent, each participant completed a short demographic and health questionnaire. Testing was completed at a central location within the retirement community by the same researcher. Physical performance-based measures included the 30-Second Chair Stand test (30-SCS) [36] and the Functional Reach test (FR) [37]. These tests were selected because they are reliable and valid tests that are easy to perform in the clinic. Cognitive assessments included the Mini-Mental State Examination as a measure of global cognition, the Clock-drawing test (CDT) [38], Trail Making Test Part B (TMT-B) [39], Flanker Compatibility Task [40], simple reaction time test, and the Digit Symbol Substitution Test (DSST) [41]. All cognitive assessments were performed on an iPad with the exception of the TMT-B and DSST, which were completed using a paper format. Physical performance and cognitive assessments were completed together in one block in the order as described above, however, to protect against order effects, the protocol was counterbalanced to have some participants performed the physical measures first while others performed the cognitive measures first.

### *2.3 Gait Assessment*

Gait speed was assessed with the 12-foot GAITRite® system, an electronic walkway designed to assess spatiotemporal gait parameters [42]. To allow for acceleration before stepping on the walkway, participants were instructed to take two steps away from the start of the walkway before each trial and then center their body facing the walkway. Participants were asked to walk at a "comfortable pace" on the GAITRite® for two trials and then were asked to walk "as fast as you can while staying safe" for two trials. Gait velocity (cm/s) was recorded for each trial. The average of the two trials (comfortable and fast) was used in statistical analyses.

### *2.4 Physical Performance Measures*

The 30-second Chair Stand Test (30-SCS) assessed lower-extremity strength by counting the number of full stands from a standard 17-inch chair without use of arms from a seated position in 30 seconds [36]. If a participant was unable to complete a single repetition without the use of hands, a score of zero was recorded. To assess standing balance, the Functional Reach (FR) test

was performed [37]. Participants were instructed to stand close to the wall without touching it and position their arm at 90 degrees of shoulder flexion with a closed fist. Participants were then instructed to "Reach as far as you can forward without taking a step". The location of the 3rd metacarpal was recorded from zero on a yardstick to the end point after reaching forward[37].

### *2.5 Cognitive Measures*

The Clock-drawing test was used to assess executive function and visuospatial function [38]. Participants were presented with a pre-drawn blank circle and asked to "draw the numbers on the circle to make it look like a clock and draw the hands to read 10 past 11 o'clock". The scoring method described by Watson and colleagues was used with a normal score ranging from 0-3 and abnormal score ranging from 4-7 [43]. The TMT-B was used to assess executive function and set-shifting [39]. Participants were instructed to connect 25 circles in an ascending pattern, without lifting the pencil, with the task of alternating between numbers and letters (numbers 1-13; letters A-L). Scores were reported as the number of seconds to complete the task, with higher scores representing greater cognitive impairment [39].

The Flanker Compatibility Task was used to assess executive function, cognitive inhibition, and selective visual attention [40]. This test was administered using the PsychLab101 iPad app [44]. Participants were instructed to decide whether they saw a square or a diamond within a display of four rings presented on the screen while ignoring any other shapes that appeared to the side of the array of rings (see Figure 1). Test trials were either congruent (the stimulus matched the stimulus to the side of the rings), incongruent (the stimulus did not match the stimulus to the side of the rings), or neither (no distractor stimulus appeared). The Flanker effect has been described as the effect of the conflict resolution on performance, such that congruent stimuli produce faster and more accurate responses than incongruent stimuli [45] In this study, the Flanker effect was calculated as the difference in mean reaction time between congruent and incongruent trials [45].

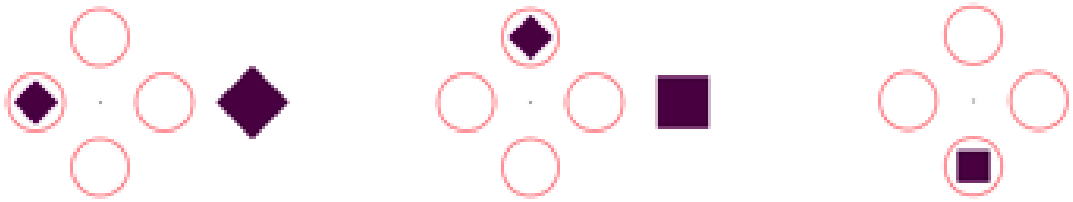

**Figure 1** Flanker compatibility task **(**Neurobehavioral Systems, 2015). Used to assess *executive function*, cognitive inhibition, and selective visual attention and administered using the PsychLab101 iPad app (Neurobehavioral Systems, Inc., Berkeley CA) [38-40]. Participants were instructed to identify if the target stimulus in the rings was a square or a diamond, while ignoring distractor stimuli outside the rings. Test trials included distractor stimuli that were either congruent (right), incongruent (middle), or neither (left).

A simple reaction time test was also administered using the PsychLab101 iPad app [44] Participants were instructed to touch the iPad screen as fast as possible when they saw the stimulus appear on the screen. The score was recorded as the average reaction time (milliseconds) for the total number of trials given. Lastly, the Digit Symbol Substitution Test was used to assess processing speed [41]. Participants matched a given number (1-9) to its corresponding symbol using the key grid at the top of the testing paper (see Figure 2). Participants were instructed to fill in as many boxes as possible in 90 seconds, in the order that they appeared. The number of boxes completed (maximum = 90) were recorded.


**Figure 2** Digit symbol substitution test [41]. Used to assess *processing speed* [41]. Following practice of the sample boxes, participants were instructed to match the correct corresponding symbol into the numbered boxes in the order that they are presented below. The number of boxes completed in 90 seconds was recorded.

### *2.6 Statistical Analysis*

Data were input into SPSS Statistical Software (Version 22.0, IBM Statistics) for analysis. Following preparatory analyses, descriptive statistics were used for sample representation and comparison to known normative data. Bivariate correlation (Pearson's *r*) analyses were examined to determine the level of association between the dependent variables of comfortable and fast gait speed and the independent variables of physical performance and cognition. Bivariate correlation was used to assist in determination of which independent variables would be included in the regression analyses.

The results from these analyses determined the independent variables used in the hierarchical linear regression models. Hierarchical linear regression models were constructed to examine the independent association of both comfortable and fast gait speeds with physical performance (30-

SCS and FR) and cognition (DSST, CDT, and Flanker effect). Also considered was the concern of multicollinearity between variables as it may inflate the size of the error terms, which could weaken the analysis by making it more difficult to reject the null hypothesis [46]. Subsequently, variables with bivariate correlations of greater than .70 should only be cautiously entered into the same analysis as these variables may be found to have multicollinearity [47] Therefore due to the high correlation between the TMT-B and DSST ($r$ = 0.70), the TMT-B was not included in regression model. In Model 1, the physical performance variables were included followed by the cognitive variables in Model 2. This approach allows separate analysis regarding contribution of each set of variables (physical performance variables and cognitive variables) to the prediction of gait speed. Alpha level was set at .05.

## 3. Results

The participant characteristics are presented in Table 1. The average age of the participants was 80.80 years (SD: 8.01) and 71% were female. The participants in the study had an average comfortable gait speed of 1.00 m/s (SD: 0.27) and an average fast gait speed of 1.41 m/s (SD: 0.37).

Bivariate correlation coefficients are reported in Table 2. Comfortable gait speed was significantly associated with the 30-SCS ($r$ = 0.54; $p$ = <0.001), FR ($r$ = 0.53; $p$ = <0.001) , TMT-B ($r$ = -0.34; $p$ = 0.004), total number of boxes completed on the DSST ($r$ = 0.48; $p$ = <0.001), and flanker effect ($r$ = -0.28; $p$ = 0.02). There was no significant association with simple reaction time; therefore, it was not included in further analyses. Fast gait speed was significantly associated with the 30-SCS ($r$ = 0.55; $p$ = <0.001), FR ($r$ = 0.44; $p$ = <0.001), TMT-B ($r$ = -0.32; $p$ = 0.007), total number of boxes completed on the DSST ($r$ = 0.57; $p$ = <0.001), and CDT ($r$ = -0.26; $p$ = 0.03). No significant association was found between fast gait speed and simple reaction time; therefore, it was not analyzed further. In the hierarchical linear regression (Tables 3 and 4), physical performance variables including the 30-SCS and FR explained 44.80% and 38.20% of the variance (adjusted $r^2$) in comfortable and fast gait speed, respectively as outlined in Model 1. The addition of cognition in Model 2 contributed significantly to both comfortable ($F$ change = 3.34; $p$ = 0.04) and fast ($F$ change = 3.78; $p$ = 0.03) gait speed. Unique predictors of comfortable gait speed in Model 2 included 30-SCS (B=1.86, $p$<0.001), FR (B=3.37, $p$=0.005), and Flanker effect (B=-0.02, $p$=0.05). This indicates that individuals who demonstrated greater lower extremity strength and balance and demonstrated greater executive function and cognitive inhibition were able to walk at a faster pace in the comfortable gait speed condition. Unique predictors of fast gait speed in Model 2 included 30-SCS (B=2.61, $p$<0.001), FR (B=3.58, $p$=0.04), and DSST (B=0.95, $p$=0.01). This indicates that individuals who demonstrated greater lower extremity strength and balance and demonstrated greater processing speed were able to walk at a faster pace in the fast gait speed condition.

**Table 1** Participant demographic characteristics (N = 66).

| Variable | Mean (SD) | Range | Reference, normal |
|---|---|---|---|
| Age, y | 80.8 (8.01) | 61-86 | |
| Comorbid Health Conditions | 3.18 (1.74) | 0-8 | |
| Falls in Past Month | 0.22 (0.54) | 0-3 | |
| Mini-Mental Status Examination Score | 28.57 (1.31) | 25-30 | < 24/30, considered abnormal |
| 30-Second Chair Stand Score, repetitions | 10.38 (6.0) | 0-25 | 9-14 repetitions |
| Functional Reach Score, in | 9.87 (2.32) | 5.08-15.17 | 10.5 inches |
| Comfortable Gait Speed, m/s | 1.0 (0.27) | 0.32-1.55 | 0.85-1.03 m/s |
| Fast Gait Speed, cm/s | 1.41 (0.37) | 0.46-2.30 | 1.59 m/s |
| Clock Drawing Test score | 1.97 (2.46) | 0-7 | >4, considered abnormal |
| Flanker Task Reaction Time, Congruent Trials | 1597.53 (550.13) | 1002.3-4331.0 | |
| Flanker Task Reaction Time, Incongruent Trials | 1701.43 (477.72) | 953.31-3458.2 | |
| Trail Making Test (Part B), time in seconds | 127.45 (81.22) | 11.31-519.00 | ~90 seconds |
| Digit Symbol Substitution Test, number completed | 42.09 (12.5) | 13-76 | |

**Table 2** Pearson correlation matrix.

| Variable | Comfortable Gait Speed, cm/s | Fast Gait Speed, cm/s |
|---|---|---|
| 30-Second Chair Stand Score | 0.54[a] | 0.55[a] |
| Functional Reach Score, in | 0.53[a] | 0.44[a] |
| Trail-Making Test (Part B) | -0.34[a] | -0.32[a] |
| Clock Drawing Test score | -0.20 | -0.26[b] |
| Flanker Effect | -0.28[b] | -0.22 |
| Digit Symbol Substitution Test, number completed | 0.48[a] | 0.52[a] |

*Notes:* [a]$p < .001$; [b]$p < .05$

**Table 3** Hierarchical linear regression summary for comfortable gait speed (cm/s).

| Independent Variable | Comfortable Gait Speed | | | | | |
|---|---|---|---|---|---|---|
| | $R^2$ | $R^2$ Change | Adjusted $R^2$ | Unstandardized B (Standard Error) | Standardized β | *P* |
| Model 1 | 0.465 | 0.465 | 0.448 | | | |
| 30-SCS | | | | 1.98 (0.4) | 0.47 | <.001 |
| FR | | | | 4.68 (1.06) | 0.42 | <.001 |
| Model 2 | 0.518 | 0.053 | 0.486 | | | |
| 30-SCS | | | | 1.86 (0.4) | 0.44 | <.001 |
| FR | | | | 3.37 (1.16) | 0.3 | 0.005 |
| DSST completed | | | | 0.35 (0.22) | 0.16 | 0.118 |
| Flanker Effect | | | | -0.02 (0.01) | -0.19 | 0.046 |

Notes: 30-SCS, 30-Second Chair Stand; FR, Functional Reach; DSST, Digit Symbol Substitution Test

**Table 4** Hierarchical linear regression summary for fast gait speed (cm/s).

| Independent Variable | Fast Gait Speed | | | | | |
|---|---|---|---|---|---|---|
| | $R^2$ | $R^2$ Change | Adjusted $R^2$ | Unstandardized B (Standard Error) | Standardized β | *P* |
| Model 1 | 0.401 | 0.401 | 0.382 | | | |
| 30-SCS | | | | 2.9 (0.62) | 0.46 | <.001 |
| FR | | | | 5.64 (1.59) | 0.35 | 0.001 |
| Model 2 | 0.468 | 0.066 | 0.433 | | | |
| 30-SCS | | | | 2.61 (0.61) | 0.42 | <.001 |
| FR | | | | 3.58 (1.73) | 0.22 | 0.042 |
| DSST completed | | | | 0.95 (0.36) | 0.32 | 0.011 |
| CDT Score | | | | 0.81 (1.78) | 0.05 | 0.651 |

Notes: 30-SCS, 30-Second Chair Stand; FR, Functional Reach; DSST, Digit Symbol Substitution Test; CDT, Clock-draw test

## 4. Discussion

The results of this study contribute to the current literature of predictors of comfortable and fast gait speed in community-dwelling older adults. It investigated the interplay of physical performance measures and specific cognitive domains that have previously been identified separately in the existing literature as variables associated with gait speed. Results indicate that lower extremity strength, balance, and executive function were unique predictors of comfortable gait speed while lower extremity strength, balance, and processing speed were unique predictors of fast gait speed. As summarized in the hierarchical linear regression model 2, these predictors explained 48.60% of the total variance in comfortable gait speed and 43.30% of the total variance

in fast gait speed. The results support the first hypothesis, that strength and balance would both be strong predictors of comfortable and fast gait speed, even after the addition of the cognitive variables. The second hypothesis was partially supported. Executive function was found to be the strongest cognitive predictor of comfortable gait speed but not fast gait speed.

These results corroborate previous research findings that lower extremity strength and balance are key predictors of gait speed. These findings add to the body of literature by providing evidence that both are predictive for both comfortable and fast gait speed. The relationship between lower extremity strength and gait speed has been demonstrated primarily using measures of dynamometry [14, 18, 27, 28]. Specifically, knee extensor, hip extensor, and ankle plantarflexor strength have all been shown to have associations with gait speed using these methods [18, 28]. In a recent study by the Mantel et al. (2018), the 30-SCS demonstrated significant predictive value for comfortable and fast gait speed. The action of rising from a chair in the 30-SCS requires the activation hip and knee extensors, allowing practicing clinicians to perform a functional assessment of lower extremity strength when gait speed deficits are present. The effect of balance on gait speed has been less studied and the available literature lacks homogeneity of balance assessments. Studies have shown positive associations between gait speed and measures of postural sway, sensory integration, and limits of stability [14-17]. While these results are encouraging, future research is needed to determine which components of balance are most influential to gait speed for specificity of intervention development.

Analyses revealed that the addition of cognitive variables showed significant contributions to the total variance in both comfortable and fast gait speeds. This contribution remained significant in spite of the large amount of variance explained by strength and balance. This additional variance explained adds to the literature by highlighting the interplay of physical and cognitive variables affecting the outcome of gait speed. Both physical and cognitive factors have a role and thus are important to consider during an exam.

In a 2016 meta-analysis of 26 cross-sectional studies investigating the relationship between gait and cognition, authors found small effect sizes in favor of positive association between gait speed and executive function and processing speed [48]. In agreement with previous cross-sectional findings [20, 21], this study found associations between comfortable gait speed and cognitive domains of executive function and processing speed. However, few studies have included fast gait speed when investigating the association between gait speed and cognition [30, 31]. This study found differences in predictors, in that executive function independently predicted comfortable gait speed while processing speed independently predicted fast gait speed. This partially supports the study hypotheses that the executive function domain would be a unique predictor of both comfortable and fast gait speed. Soumare and colleagues (2009) found that processing speed was more specifically associated with fast gait speed than executive function after controlling for confounders. In contrast, another study found that executive function was independently associated with fast gait speed, but not comfortable gait speed, after adjusting for cofounders [31]. These mixed findings highlight the complexity of cognitive processes' that are required to adapt to a less-automatic physical performance task such as fast walking. Multiple studies have demonstrated the influence of higher cognitive processes on gait under varying conditions such as fast walking or dual-task walking [21, 49, 50]. Additionally, these differences may be explained by the heterogeneity among studies investigating cognition and gait speed, with variations and overlap in the interpretation of the cognitive domain measured. In contrast to previous studies

investigating cognition and gait speed, the current study also included physical performance variables which may have contributed to the non-significance of some cognitive measures in the final regression model, despite significance found in bivariate correlations.

The interplay found between physical performance and cognition urges clinicians and researchers to investigate and evaluate gait speed with an interdisciplinary approach. As stated previously, gait speed has been recognized as a useful screening tool to offer insight into future health status functional decline, and fall risk [5]. This study suggests that if an older adult was screened using a gait speed assessment and was found to have gait speed deficits, further assessment of both physical and cognitive function is warranted to identify the most appropriate therapeutic interventions. A geriatric patient is often under the care of multiple healthcare providers who have the ability to collaborate to optimize the health and functioning of an older adult. The simplicity of administering a gait speed assessment allows many healthcare professionals to perform a screening and evaluate the need for further assessment of gait speed predictors identified in current literature. Physical impairments of strength and balance may be evaluated and treated by a professional such as a physical therapist, while cognitive impairments are better served by a professional such as a physician or speech language pathologist.

This study is not without limitations. The sample was very homogenous, limiting the generalizability of the findings. Additionally, while the sample size was adequate to address the particular research question regarding the interplay between physical performance and cognition on gait speed, a larger sample would allow sub-analyses to be performed based on gender or age to determine any impact those variables may have on these findings as these variables may have some confounding effect on the interplay between cognitive and physical performance variables. Additionally, a larger sample size would allow more sophisticated statistics, such as structural equation modeling, to allow a better understanding of the relationships that have been identified in this study.

## 5. Conclusions

This study suggests that both comfortable and fast gait speed are primarily predicted by strength and balance. Many clinicians are qualified to use gait speed as a screening tool for older adults. When a gait speed deficit is found, commonly used clinical measures of functional lower extremity strength and balance can be used to further assess the source of the impairment. The interplay found between physical performance and cognition emphasizes the importance of interdisciplinary care. Future studies should investigate the longitudinal associations between gait speed, cognition, and physical performance variables to better understand the directionality of these relationships.

## Author Contributions

***Ashleigh Trapuzzano*** was involved in project conceptualization, project design, participant recruitment, data collection, interpretation of the results, and dissemination including writing this manuscript.

***Sara Chizmar*** was involved in project conceptualization, project design, participant recruitment, data collection, interpretation of the results, and dissemination including writing this manuscript.

***Lauren Haffke*** was involved in project conceptualization, project design, participant recruitment, data collection, interpretation of the results, and dissemination including writing this manuscript.

***Nicole Dawson*** is the Director of the Innovative Mobility Initiative (IMOVE) Lab at the University of Central Florida and was the senior researcher on the project. She oversaw all aspects of the project and completed the statistical analysis.

**Competing Interests**

The authors have declared that no competing interests exist.

**References**

1. United Nations. Ageing [Available from: http://www.un.org/en/sections/issues-depth/ageing/.
2. The United States Census Bureau. The Nation's Older Population Is Still Growing 2017 [Available from: https://www.census.gov/newsroom/press-releases/2017/cb17-100.html.
3. Peel NM, Kuys SS, Klein K. Gait speed as a measure in geriatric assessment in clinical settings: A systematic review. J Gerontol A Biol Sci Med Sci. 2013; 68: 39-46.
4. Goldberg A, Schepens S. Measurement error and minimum detectable change in 4-meter gait speed in older adults. Aging Clin Exp Res. 2011; 23: 406-412.
5. Fritz S, Lusardi M. White paper:"walking speed: The sixth vital sign". J Geriatr Phys Ther. 2009; 32: 2-5.
6. Cesari M, Kritchevsky SB, Penninx BW, Nicklas BJ, Simonsick EM, Newman AB, et al. Prognostic value of usual gait speed in well-functioning older people—results from the health, aging and body composition study. J Am Geriatr Soc. 2005; 53: 1675-1680.
7. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. JAMA. 2011; 305: 50-58.
8. Verghese J, Wang C, Holtzer R. Relationship of clinic-based gait speed measurement to limitations in community-based activities in older adults. Arch Phys Med Rehabil. 2011; 92: 844-846.
9. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, et al. Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci. 2000; 55: M221-M231.
10. Artaud F, Singh-Manoux A, Dugravot A, Tzourio C, Elbaz A. Decline in fast gait speed as a predictor of disability in older adults. J Am Geriatr Soc. 2015; 63: 1129-1136.
11. Van Kan GA, Rolland Y, Andrieu S, Bauer J, Beauchet O, Bonnefoy M, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging. 2009; 13: 881-889.
12. Callisaya ML, Blizzard L, McGinley JL, Srikanth V. Risk of falls in older people during fast-walking–the TASCOG study. Gait Posture. 2012; 36: 510-515.
13. Best JR, Liu-Ambrose T, Boudreau RM, Ayonayon HN, Satterfield S, Simonsick EM, et al. An evaluation of the longitudinal, bidirectional associations between gait speed and cognition in older women and men. J Gerontol A Biol Sci Med Sci. 2016; 71: 1616-1623.

14. Aranda-García S, Busquets A, Planas A, Prat-Subirana JA, Angulo-Barroso RM. Strength, static balance, physical activity, and age predict maximal gait speed in healthy older adults from a rural community: A cross-sectional study. J Aging Phys Act. 2015; 23: 580-587.
15. Mantel A, Trapuzzano A, Chizmar S, Haffke L, Dawson N. An investigation of the predictors of comfortable and fast gait speed in community-dwelling older adults. J Geriatr Phys Ther. 2019; 42: E62-E68.
16. Xie YJ, Liu EY, Anson ER, Agrawal Y. Age-related imbalance is associated with slower walking speed: An analysis from the National Health and nutrition examination survey. J Geriatr Phys Ther. 2017; 40: 183-189.
17. Callisaya ML, Blizzard L, Schmidt MD, McGinley JL, Lord SR, Srikanth VK. A population-based study of sensorimotor factors affecting gait in older people. Age Ageing. 2009; 38: 290-295.
18. Bean JF, Leveille SG, Kiely DK, Bandinelli S, Guralnik JM, Ferrucci L. A comparison of leg power and leg strength within the InCHIANTI study: Which influences mobility more? J Gerontol A Biol Sci Med Sci. 2003; 58: M728-M733.
19. Hicks GE, Shardell M, Alley DE, Miller RR, Bandinelli S, Guralnik J, et al. Absolute strength and loss of strength as predictors of mobility decline in older adults: The InCHIANTI study. J Gerontol A Biol Sci Med Sci. 2011; 67: 66-73.
20. Martin KL, Blizzard L, Wood AG, Srikanth V, Thomson R, Sanders LM, et al. Cognitive function, gait, and gait variability in older people: A population-based study. J Gerontol A Biol Sci Med Sci. 2012; 68: 726-732.
21. Killane I, Donoghue OA, Savva GM, Cronin H, Kenny RA, Reilly RB. Relative association of processing speed, short-term memory and sustained attention with task on gait speed: A study of community-dwelling people 50 years and older. J Gerontol A Biol Sci Med Sci. 2014; 69: 1407-1414.
22. Atkinson HH, Rosano C, Simonsick EM, Williamson JD, Davis C, Ambrosius WT, et al. Cognitive function, gait speed decline, and comorbidities: The health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2007; 62: 844-850.
23. Miljkovic N, Lim JY, Miljkovic I, Frontera WR. Aging of skeletal muscle fibers. Ann Rehabil Med. 2015; 39: 155-162.
24. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: The health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2006; 61: 1059-1064.
25. Cawthon PM, Fox KM, Gandra SR, Delmonico MJ, Chiou CF, Anthony MS, et al. Do muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults? J Am Geriatr Soc. 2009; 57: 1411-1419.
26. Buchner DM, Larson EB, Wagner EH, Koepsell TD, DE LATEUR BJ. Evidence for a non-linear relationship between leg strength and gait speed. Age Ageing. 1996; 25: 386-391.
27. Mangione KK, Craik RL, Lopopolo R, Tomlinson JD, Brenneman SK. Predictors of gait speed in patients after hip fracture. Physiother Can. 2008; 60: 10-18.
28. Muehlbauer T, Granacher U, Borde R, Hortobágyi T. Non-discriminant relationships between leg muscle strength, mass and gait performance in healthy young and old adults. Gerontology. 2018; 64: 11-18.
29. Cohen JA, Verghese J, Zwerling JL. Cognition and gait in older people. Maturitas. 2016; 93: 73-77.

30. Soumaré A, Tavernier B, Alpérovitch A, Tzourio C, Elbaz A. A cross-sectional and longitudinal study of the relationship between walking speed and cognitive function in community-dwelling elderly people. J Gerontol A Biol Sci Med Sci. 2009; 64: 1058-1065.
31. Ble A, Volpato S, Zuliani G, Guralnik JM, Bandinelli S, Lauretani F, et al. Executive function correlates with walking speed in older persons: The InCHIANTI study. J Am Geriatr Soc. 2005; 53: 410-415.
32. Holtzer R, Verghese J, Xue X, Lipton RB. Cognitive processes related to gait velocity: Results from the Einstein Aging Study. Neuropsychology. 2006; 20: 215.
33. Callisaya ML, Blizzard CL, Wood AG, Thrift AG, Wardill T, Srikanth VK. Longitudinal relationships between cognitive decline and gait slowing: The Tasmanian Study of Cognition and Gait. J Gerontol A Biol Sci Med Sci. 2015; 70: 1226-1232.
34. Watson N, Rosano C, Boudreau R, Simonsick E, Ferrucci L, Sutton-Tyrrell K, et al. Executive function, memory, and gait speed decline in well-functioning older adults. J Gerontol A Biol Sci Med Sci. 2010; 65: 1093-1100.
35. Cohen J. A power primer. Psychol Bull. 1992; 112: 155.
36. Rikli RE, Jones CJ. Development and validation of a functional fitness test for community-residing older adults. J Aging Phys Act. 1999; 7: 129-161.
37. Duncan PW, Weiner DK, Chandler J, Studenski S. Functional reach: A new clinical measure of balance. J Gerontol. 1990; 45: M192-M197.
38. Juby A, Tench S, Baker V. The value of clock drawing in identifying executive cognitive dysfunction in people with a normal Mini-Mental State Examination score. Can Med Assoc J. 2002; 167: 859-864.
39. Arbuthnott K, Frank J. Trail making test, part B as a measure of executive control: Validation using a set-switching paradigm. J Clin Exp Neuropsychol. 2000; 22: 518-528.
40. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept Psychophys. 1974; 16: 143-149.
41. Kaufman AS. Test Review: Wechsler, D. Manual for the wechsler adult intelligence scale, revised. New York: Psychological Corporation, 1981. J Psychoeduc Assess. 1983; 1: 309-313.
42. GAITRite. GAITRite Electronic Walkway Technical Reference. Franklin, NJ: CIR Systems, Inc; 2016. Available from: http://gaitrite.legacy.si-servers.com/WI-02-15_Technical_Reference_T.pdf.
43. Watson YI, Arfken CL, Birge SJ. Clock completion: An objective screening test for dementia. J Am Geriatr Soc. 1993; 41: 1235-1240.
44. Neurobehavioral Systems. Psych Lab 101. 2.02 ed. Berkeley, CA: Neurobehavioral Systems, Inc; 2015.
45. Holtzer R, Mahoney J, Verghese J. Intraindividual variability in executive functions but not speed of processing or conflict resolution predicts performance differences in gait speed in older adults. J Gerontol A Biol Sci Med Sci. 2013; 69: 980-986.
46. Bobko P. Correlation and regression: Applications for industrial organizational psychology and management. Sage; 2001.
47. Tabachnick BG, Fidell LS, Ullman JB. Using multivariate statistics. Pearson Boston, MA; 2007.
48. Demnitz N, Esser P, Dawes H, Valkanova V, Johansen-Berg H, Ebmeier KP, et al. A systematic review and meta-analysis of cross-sectional studies examining the relationship between mobility and cognition in healthy older adults. Gait Posture. 2016; 50: 164-174.

49. Lowry KA, Brach JS, Nebes RD, Studenski SA, VanSwearingen JM. Contributions of cognitive function to straight-and curved-path walking in older adults. Arch Phys Med Rehabil. 2012; 93: 802-807.
50. Coppin AK, Shumway-Cook A, Saczynski JS, Patel KV, Ble A, Ferrucci L, et al. Association of executive function and performance of dual-task physical tests among older adults: Analyses from the InChianti study. Age Ageing. 2006; 35: 619-624.

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Review Article

# Physical Activity's Impact on Quality of Life in Older Adults with Dementia: A Systematic Review

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**Abstract**

Individuals with dementia frequently report poor quality of life (QOL), which declines as their disease progresses. Some evidence suggests that physical activity may help maintain cognitive function in older age, but it is unclear whether physical activity affects quality of life in older adults with dementia. The purpose of this review paper is to explore whether and how physical activity impacts QOL in patients with diagnosed dementia in different residential settings. To conduct this systematic review, the following search terms were inputted into the search bars of three databases:(dementia OR Alzheimer) AND (walking OR physical activity OR exercise OR fitness) AND (community OR nursing home OR independent living OR green care) AND (Quality of Life). A total of ten articles met the study inclusion criteria. Several studies reported a positive correlation between physical activity intervention programs and QOL outcome measures, pertaining to socialization and positive emotions, and an increase in physical endurance capacity among program participants. However, most results were not statistically significant. We conclude that more large studies need to be conducted in order to establish whether there is a significant positive dose-

response relationship between physical activity intervention programs and QOL measures among individuals with diagnosed dementia.

**Keywords**
Dementia; Alzheimer's disease; physical activity; quality of life; nursing home; community dwelling

## 1. Introduction

The current prevalence of Alzheimer's disease in the United States is 5.8 million individuals [1]. Of these, an estimated 5.6 million are aged 65 years or older. This number is expected to continue to rise in the next decades due to the increasing number of older individuals among the U.S. population. Studies estimate that by 2025, there will be a 27% increase in the number of individuals older than 65 living in the United States with Alzheimer's disease [1].

The number of individuals living with Alzheimer's disease is not expected to decline in the near future, therefore, it is important to consider its overall costs on our healthcare system. An estimated $290 billion was spent on dementia care in long-term care and hospice in 2019 alone. Government spending through Medicare and Medicaid covered approximately 67% of the total health care cost of dementia. Out of pocket payments, with its direct impact on family finances, make up to an estimated 22% [2].

About 70% of individuals older than 65 living with dementia reside in the community, a dramatic difference from the 98% of those not diagnosed with dementia [2]. Many of the dementia diagnosed individuals receive some form of paid care. From 2017 to 2018, the average cost of assisted living ranged from $45,000 to $48,000 per year and nursing home care ranged from $85,775 to $89,297 a year [3, 4]. There is no public program, aside from Medicaid, that will pay for long term nursing home care [2].

Actively managing dementia has been shown to lead to an improvement in quality of life (QOL), including participation in meaningful activities and opportunities to socialize with other dementia diagnosed patients [5]. Additionally, studies suggest that physical activity may improve cognitive function for dementia patients [6, 7]. The purpose of our review is to examine whether physical activity impacts QOL in patients diagnosed with dementia, and also to explore whether the residential setting where these individuals live (nursing home or community-dwelling) play a role in the relationship between physical activity and QOL.

## 2. Materials and Methods

### *2.1 Methods*

We input the following search terms into the PubMed, EMBASE, EBSCO (PyschInfo, Ageline, and CINAHL) search bars: (dementia OR Alzheimer) AND (walking OR physical activity OR exercise OR fitness) AND (community OR nursing home OR independent living OR green care) AND (Quality of Life). This search was conducted in September 2018 and contains articles from the year 2000 to the month the search was conducted.

The PubMed search resulted in 526 peer reviewed articles. Applying study criteria, the articles were then reviewed for relevance to our study. Articles that did not mention dementia, interventions involving physical activity, or no mention of the association of physical activity with QOL in dementia diagnosed patients were excluded from our study. From the PubMed search, seven articles were retained for our systematic review.

Our EBSCO search, in which we gathered articles from PsychInfo, Ageline and CINAHL yielded 243 articles. We added filters in which we selected results for which our search terms were present in the Abstract portion of the article. We also added filters for the articles to be peer reviewed, journal articles, and in English. There were 120 articles excluded since they were duplicates from PubMed and Embase. Of the remaining 123 articles, 122 were excluded due to the same criteria that was used with the PubMed articles. Zero articles met the criteria to the be included.

In EMBASE, we had a search result of 384 articles. We had our filters set to only search for our key terms in the title, Abstract, and author keywords portions of the journal articles. 17 of the articles were excluded since they were duplicates. Of the 367 articles that remained, three met our criteria to be included in our systematic review. Figure 1 provides a visual of our reasons for exclusion.

A total of ten articles were included in our systematic review.

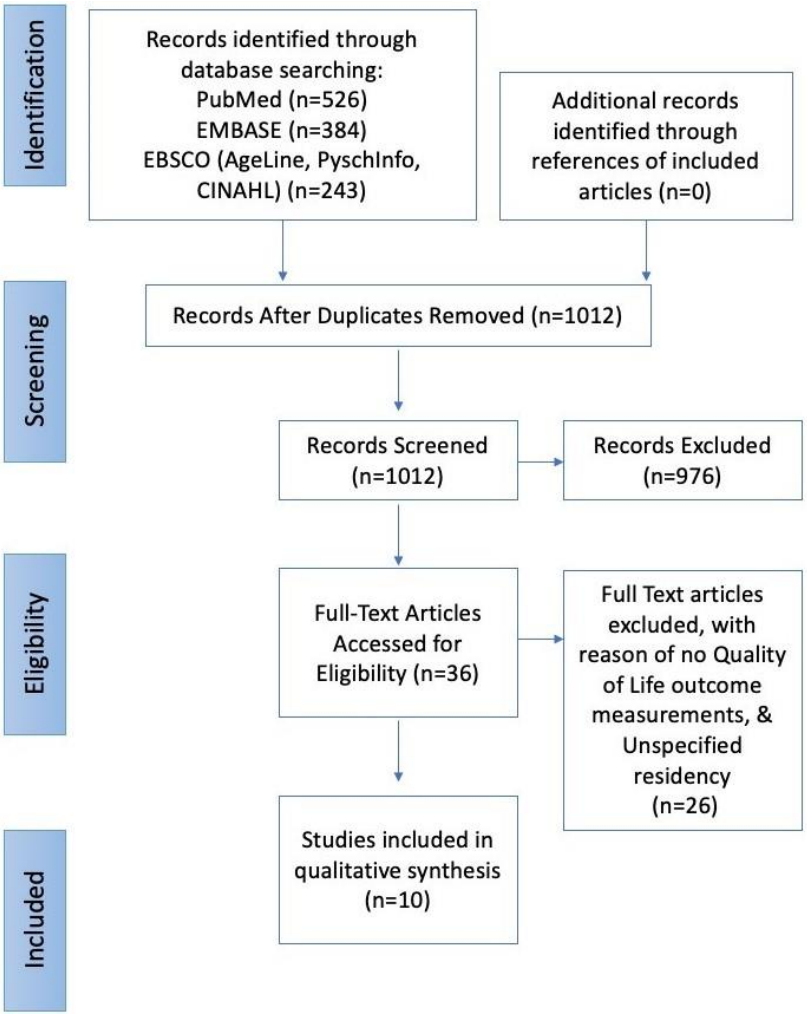


**Figure 1** Database Search History with Exclusion Criteria Outlined.

### *2.2 Inclusion Criteria*

Studies included in our systematic review were required to have examined the correlation between physical activity and the QOL of individuals living with dementia as one of their main outcomes, there needed to be a QOL measurement scale present in the study with both baseline and end of study measurements. The study needed to explicitly state whether their study subjects lived in nursing homes or were community dwellers.

### *2.3 Exclusion Criteria*

Studies that were not examining dementia, physical activity, QOL, or the experiences of the individual living with dementia were excluded from this systematic review. Additionally, due to our interest in study results, uncompleted studies were excluded.

### *2.4 Quality Assessment*

The Jadad Scale was used to evaluate the quality of each of the randomized controlled trials. Items on the scale are randomization, blinding, and whether or not the study accounts for withdrawals and dropouts (Table 1). The scale is rated from zero to five with a score of five being a study of high quality [8].

For non- randomized studies, we used the Methodological Index for Non-Randomized Studies (MINORS) instrument to assess the quality of each study [9] (Table 2).

**Table 1** Quality Assessment for Randomized Controlled Trials using the Jadad Scale [8].

| Item | Lamb et al. [10] | Ballard et al. [11] | Henskens et al. [12] | Hoffmann et al. [13] | Telenuis et al. [14] | Tanaka et al. [15] |
|---|---|---|---|---|---|---|
| Randomization Mentioned | 1 | 1 | 1 | 1 | 1 | 1 |
| Randomization Appropriate | 0 | 1 | 1 | 1 | 1 | 1 |
| Blinding Mentioned | 0 | 1 | 1 | 1 | 1 | 1 |
| Blinding Appropriate | 0 | -1 | -1 | -1 | -1 | -1 |
| Withdrawals and Dropouts Mentioned | 1 | 1 | 1 | 1 | 1 | 1 |
| Total | 2 | 3 | 3 | 3 | 3 | 3 |

**Table 2** Quality Assessment for Non-Randomized Trials using the MINORS.

| MINORS [9] | La Rue et al. | Henskens et al. | Taylor et al. | Olsen et al. |
|---|---|---|---|---|
| Clearly stated aim | 1 | 1 | 1 | 1 |
| Inclusion of consecutive patients | 0 | 1 | 0 | 1 |
| Prospective collection data | 1 | 1 | 1 | 0 |
| Endpoints appropriate to the aim of the study | 1 | 1 | 1 | 1 |
| Unbiased assessment of the study endpoint | 0 | 0 | 0 | 0 |
| Follow-up period appropriate to the aim of the study | 1 | 1 | 1 | 0 |
| Loss to follow up less than 5% | 0 | 0 | 0 | 0 |
| Prospective calculation of the study size | 0 | 0 | 0 | 0 |
| An adequate control group | N/A | 1 | 0 | N/A |
| Contemporary groups | N/A | 1 | 0 | N/A |
| Baseline equivalence of groups | N/A | 0 | 0 | N/A |
| Adequate statistical analyses | N/A | 1 | 1 | N/A |
| Total | 4 | 8 | 5 | 3 |

### *2.5 QOL Scales*

There are several scales used to assess QOL in research. Table 3 lists the QOL scales utilized specifically in the studies included in this review alongside the number of items measured, subscales and scoring for each QOL scale. The number of items measured range from five to 37. While the range of items vary, the topics covered in the scales are similar. The QUALIDEM, Quality of Life in Dementia (QOL-D), and DEMQOL-PROXY scales each have two topics that ask specifically about “positive affect/emotion” and “negative affect/emotion” [16, 17, 19, 20]. The SF-36 HRQL, Qualidem, and QUALID explicitly address social interaction [16-18, 21]. Additionally, the QUALID and Qualidem were administered by caregivers who work closely with the subjects observed [10-12]. The QUALID, Qualidem, and DEMQOL-PROXY state in their studies that they use a Likert Rating Scale for their scale scoring [16, 17, 20, 22].

**Table 3** Overview of QOL Scales.

| SCALE | ITEMS | SUBSCALES | SCORING |
|---|---|---|---|
| Quality of Life in Late Stage Dementia (QUALID) [18] | 11 | Smiles, appears sad, cries, has facial expression of discomfort, appears physically uncomfortable, verbalizations suggest discomfort, irritable or aggressive, enjoys eating, enjoys touching/being touched, enjoys interacting with others, appears calm and comfortable | The lower the score the better the QOL (11-55) |
| QUALIDEM [16, 17] | 37 | Care relationship, positive affect, negative affect, restless tense behavior, positive self-image, social relations, social isolation, feeling at home, having something to do | The higher the score the better the QOL (0-27) |
| QOL-AD (Quality of Life in Alzheimer's disease) [22] | 13 | Physical health, energy, mood, living situation, memory, family, marriage, friends, self as a whole, | The higher the score the better the QOL (13-52) |
| European Quality of Life–5 Dimensions (EQ-5D) [23] | 5 | Mobility, self-care, usual activities, pain/discomfort, anxiety/depression | The higher the score the better the QOL |
| Qol-D (Quality of Life in Dementia) [19] | 31 | Positive affect, negative affect and actions, ability of communications, restlessness, attachment with others, spontaneity and activity | Scoring Unspecified |
| DEMQOL-PROXY (DEMQOL Performed By Caregiver) [24] | 31 | Cognition, negative emotion, daily activities, positive emotion, appearance, non- and -cross- loaders | The higher the score the better the QOL (31-124) |

Though there are similarities between the scales, there are a few key differences that set these scales apart. The Qualidem is used to examine subjects with mild to severe dementia and is scored by adding the mean scores of the nine subscales together as opposed to the other studies in which the scores of the items are added together [16, 17]. The QOL-D used in the study for this systematic review was meant for use in evaluating subjects in Japan and is the only scale to include an item pertaining to living situation [22].

## 3. Results

### *3.1 Comparison of Study Designs*

Of the ten studies which met the inclusion criteria (see Table 4), six studies were randomized controlled trials, [10-15] two studies were quasi-experimental studies [25, 26], one study was a cohort study [27], and one study was a cross sectional study [28].

Five of the studies observed community dwelling individuals [10, 13, 15, 25, 27], four studies observed nursing homes [10, 11, 14, 26], one study compared community dwelling individuals to nursing home residents [28].

The sample sizes for the studies ranged from 33 participants to 494 participants, there were no differences in sample sizes by living situations. The trial length ranged from three months to 20 months. The longest trial time of 20 months was observing community dwelling participants [25].

Aside from two studies that only examined mild dementia and mild Alzheimer's disease, the other studies observed varying stages of dementia ranging from mild to severe. Mild dementia is defined by the Clinical Dementia Rating (CDR) scale as an individual with moderate memory loss, moderate difficulty with time relationships, moderated difficulty in handling problems, similarities and differences, however, their social judgement is typically maintained, unable to function independently but still engaged, and mild but definite impairment of function at home. Moderate dementia is defined as severe memory loss in that only highly learned material is retained and new material is rapidly lost, severe difficulty with time relationships, severely impaired handling problems, similarities, and differences, at this stage judgement is typically impaired, and only simple chores are preserved. Lastly, the severe stage of dementia is defined by severe memory loss (only fragments remain, oriented to person only, inability to make judgements or solve problems, cannot be taken outside of family home and there is no significant function in home) [29].

**Table 4** Summary characteristics of studies investigating the role of physical activity for promoting QOL in individuals with dementia or mild cognitive impairment.

| Authors | Location | Living Situation | QOL Measure | Stage of AD/Dementia | n | Study Type | Study Length | Results |
|---|---|---|---|---|---|---|---|---|
| La Rue et al. [25] | Wisconsin | Community Dwelling | QOL-AD | Mild Dementia | 64 | Quasi-Experimental: volunteer pairs met 2x/week for exercise, language engagement, and social outing/volunteer work, no control group | 20 months | No significant change in QOL were observed |
| Lamb et al. [10] | England | Community Dwelling | EQ - 5D | Mild to Moderate Dementia | 494 | Randomized Controlled Trial: supervised group aerobic/resistance exercise sessions 2x/week (plus weekly unsupervised exercise session at home) for 4 months; then 8 months unsupervised exercise program. The control group received usual care. | 12 months | Intervention program did not improve QOL. Although physical fitness increased, cognitive function decreased in the treatment group more than control group over the 12-month study period. |
| Henskens et al. [26] | Netherlands | Nursing Home | Qualidem | Moderate to Severe Dementia | 141 | Quasi- Experimental: 2 nursing homes were non-randomly assigned as either the intervention or control (as usual care). The intervention included training on physical activity and independence in everyday activities | 12 months | No significant impact on overall QOL, but there was an increase in positive self-image for those in the intervention group after 12-month follow-up. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ballard et al. [11] | United Kingdom | Nursing Home | DEMQOL - PROXY | Mild to Severe Dementia | 277 | Randomized Controlled Trial (4 groups, factorial design): an antipsychotic (medication) review intervention, an exercise intervention targeting 1 h/week individualized plan, a social interaction intervention for at least 1-h/week, and person-centered care only (control) | 9 months | There was significant improvement in QOL for those receiving the social intervention. For the exercise intervention, there was no impact on overall QOL, but improvement in positive emotion |
| Henskens et al. [12] | Netherlands | Nursing Home | Qualidem | Moderate to Severe | 87 | Randomized Controlled Trial (4 groups): aerobic/strength training 3x/week and activities of daily living training, social activity 3x/week and activities of daily living training, aerobic/strength training and care-as usual, social activity and care-as-usual | 6 months | There was no effect of aerobic/strength training on OL, but ADL training improved QOL constructs, including care relationship, positive self-image, and feeling at home |
| Taylor et al. [27] | Australia | Community Dwelling | QOL - AD | Mild to Moderate Dementia | 33 | Quasi-Experimental: all participants were offered a home based individual tailored exercise program; there was no control group | 6 months | There was no significant change in QOL post-intervention |
| Hoffmann et al. [13] | Denmark | Community Dwelling | EQ - 5D | Mild Alzheimer's | 200 | Randomized Controlled Trial: intervention group enrolled in supervised exercise group 3x a week; control group received treatment as usual | 4 months | No significant changes in HRQOL for the intervention group versus control. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Telenuis et al. [14] | Oslo, Norway | Nursing Home | QUALID | Mild to Moderate Dementia | 170 | Randomized Controlled Trial: the intervention was an intensive strength and balance session 2x/week; the control group participated in leisure activities 2x/week (reading, games, music, and conversation) | 3 months | No significant change in QUALID score in intervention versus control, but the intervention group reported more significant decrease in feelings of apathy compared to controls |
| Tanaka et al. [15] | Japan | Community Dwelling | QOL-D | Mild to Severe Dementia | 60 | Randomized Controlled Trial (3 groups): a 1-h group intervention 2x/week, a 20-min personal training intervention 2x/week, and control group receiving usual care | 3 months | QOL scores did not change in the intervention groups compared to the control group |
| Olsen et al. [28] | Norway | Community Dwelling & Nursing Home | QUALID | Mild to Severe Dementia | 193 | Cross Sectional | N/A | Home Dwelling participants participated in more moderate activity and had higher QOL than nursing home individuals. Physical activity was not significantly associated with QOL after accounting for residence. |

### *3.2 QOL Outcome Measure*

Six distinct QOL scales were used in these studies. Two studies used the QUALID scale [14, 28], two studies assessed their QOL outcome using the Qualidem scale [12, 26], two studies used the QOL-AD scale [25, 27], two used the EQ-5D scale [10, 13], one used the QOL-D scale [15], and one used the DEMQOL-PROXY scale [11].

### *3.3 Main Findings*

One study found a linkage between physical activity and QOL [28]. The study by Olsen et al. examined dementia patients residing in nursing homes and those living in the community using a cross sectional study design. The authors found that individuals in nursing homes were significantly less active and spent the majority of their time involved in sedentary activities compared to community dwelling individuals, as measured by an actigraphy device. The nursing home dwelling dementia patients reported lower QOL. After performing a regression analysis, the study demonstrated place of residency had a significant role in lower QOL, after controlling for confounding of age, gender, social encounters, use of walking aids, moderate physical activity level, light exposure, and medication. The study further concluded that, when looking at change in QOL over time, residency accounted for 25% of the change in QOL among subjects with moderate dementia (p-value = 0.039). Community dwelling subjects living with dementia had a mean change in QOL of -0.38 compared to the mean change in QOL of 1.73 in nursing home resident living with dementia. Baseline QUALID Score and institutionalization significantly predicted the change in QUALID after a six months period ($p<0.05$) [28].

The remaining physical activity intervention studies did not observe significant changes in the QOL of dementia diagnosed patients following the intervention [10-15, 25-27]. There were improvements in QOL scale categories pertaining to positive self-image, apathy, and positive emotion [11, 14, 26]. One study observed that the intervention group scored significantly better compared to the control group on the Qualidem's positive self-image subscale following a 12 month period (p-value < 0.001) [26]. Another study found the difference between the physical activity intervention group and the control group to be borderline statistically significant for apathy (p-value = 0.048) [14]. Ballard et al.'s study found an improvement in positive emotion for the exercise arm of their intervention (p-value < 0.0001). Additionally, in their social intervention there was a significant improvement in QOL (p-value = 0.04) [11]. All three of these studies observed residents in nursing homes [11, 14, 26].

## 4. Discussion

One study used in our systematic review identified a positive correlation between participation in intervention programs and QOL outcome measure while other studies reported positive associations with particular aspects of QOL, but the association with total QOL was not significant [10-13, 26]. It is unclear why the relationship between physical activity and QOL were observed for some studies and not others. Sensitivity analyses from studies may shed some light.

Three studies observing community dwelling subjects demonstrate a possible relationship between physical activity tolerance with the change in QOL [10, 13, 25]. Participants with mild Alzheimer's disease who attended more sessions had higher ratings of overall QOL [13]. A few

studies also reported that individuals who achieved higher levels of exercise as the intervention progressed, had higher mean change in QOL [10, 25]. These findings suggest the potential for certain individuals who can handle more intensive exercise benefitting more from a physical activity intervention, particularly for those with mild dementia since two of the three studies only observed patients with mild Alzheimer's or mild dementia [13, 25]. These findings could point future studies in the direction of studying the characteristics of individuals who benefit from exercise interventions to better understand which individuals to target in policy making and program implementation.

From our systematic review, one study suggests a positive relationship between QOL in dementia diagnosed individuals and physical activity [28]. While physical activity does improve some aspects of QOL, there is insufficient evidence that this leads to an improvement in overall QOL [12, 13, 15, 27]. There may be significant improvement in QOL for participants enrolled in programs that encourage social interactions with interventions that were personalized to include individual interests and life histories [11]. The studies that saw improvement in particular aspects of QOL relating to positive emotions were all studies observing nursing home residents [11, 12, 26]. In future research, it will be important to examine how a multidimensional intervention that incorporates both social interaction and physical activity could significantly improve QOL as opposed to an intervention that solely focuses on physical activity.

Participation in a physical activity intervention led to an increase for particular QOL outcomes, as measured by belonging, feeling more at home, positive self-image, positive effect on QOL, apathy, and agitation [12]. One study observed that performing familiar activities that were representative of their former home life made participants feel more at home [12]. Social interaction in combination with Person Centered Care significantly improved QOL [11]. Observation of the importance of group membership to maintain and promote well-being was reported [15]. Among nursing home residents, physical activity may reduce apathy and agitation [14].

Although our findings demonstrate possible positive implications on QOL from physical activity interventions, the quality of the studies included in our systematic review were weak to moderate. The Jadad scale was applied to our randomized controlled trials, each of the six studies scored a two or a three due to their inability to double blind [8, 10-15]. The MINORS instrument was used for nonrandomized studies, these studies ranged from three to eight [9, 25-28]. The study with a score of eight was the highest quality study of our included studies [26].

### *4.1 Strengths and Limitations*

We did not identify differences in study methods between studies that reported an effect on QOL from those that did not. The study length, QOL measurement scales, and study types varied in both groups of studies. The QOL measurement scales may not be comparable due to the varying number of items and inclusion of different QOL aspects. Additionally, there may be relevant studies not captured in this review since the researchers did not look at overall QOL specifically but aspects of QOL were assessed during the study. Some of these aspects may be more sensitive to individuals living with dementia. In their reported study limitations, several authors drew attention to the reduced generalizability of their interventions to a broader population because some studies included or limited participants based on the severity of dementia and other studies

did not differentiate severity of dementia among study subjects [15, 27]. Another major limitation included lack of control groups in some of the intervention studies. In the majority of the studies, the control arm was a group of participants who were receiving the standard level of care, but it is unclear how intervention groups would compare to individuals receiving no care. Several of the studies included a social interaction component that may have additionally impacted the results of the overall QOL since Ballard et al. found that their social interaction intervention group had better overall QOL results than the physical interaction group [10-12, 15, 25, 26]. Lastly, in a study examining wellbeing in the elderly population, the authors posed the question of whether or not wellbeing, which is similar to our definition of QOL, is a stable concept and whether the current QOL measures are not sensitive enough to capture minor changes in individual wellbeing [30].

Finally, studies that did not specify the stage of dementia of their participants were more likely to observe some improvement in QOL as a result of their intervention compared to studies that exclusively examined participants in a particular dementia stage [10, 11, 28]. This finding suggests that more research should be done to specify a subpopulation of individuals living with dementia in which a physical activity intervention would be most beneficial.

A strength of this review is that it highlights the complexity of conducting research among a population of subjects living with a condition that is difficult to define in terms of severity, varying standards of care, and comorbid conditions. It is at times challenging to categorize this population since dementia is such a heterogeneous disease and individuals with dementia frequently have multiple comorbidities [31].

### *4.2 Implications*

Alzheimer's disease not only burdens the individuals living with the disease but also their families and caregivers. In terms of disability -adjusted life years (DALYs), the unit for measuring disease burden, Alzheimer's disease ranked sixth on a 2016 list of most burdensome diseases in the United States [2]. This is a six-rank increase from the 1990 list. The increase in disease burden contributes to the urgent need for large randomized controlled studies to examine the role of a range of physical activity interventions on the QOL of individuals living with dementia. Improving QOL can be a factor that contributes to reducing the disease burden on, not only the individual, but also care-giving burden on their families and caregivers.

This systematic review's purpose was to examine if and how physical activity impacts the QOL of dementia diagnosed patients in nursing homes compared to those residing in the community. Results from our review of the literature showed that in some intervention studies in nursing home residents, physical activity led to improvements in some aspects of QOL, though total QOL was not significantly improved overall. Nursing homes may be promising sites for physical activity program implementation in individuals with dementia because it could be easier to ensure study adherence [11, 12, 26].

In the United States, community dwelling and traditional nursing homes are the primary living situations for individuals living with dementia, but other options of care could be considered. In the Netherlands and Canada, there has been a shift towards a different form of "nursing home" care called "dementia villages." These villages, designed for individuals living with severe dementia, provide individuals with a sense of independence that is different from a traditional nursing home. The center resembles a small town where residents are allowed to roam independently –

partaking in activities of their choosing. Meanwhile, hidden cameras and discreet staff ensure the safety of residents. The rationale for creating such a living environment was to provide individuals with the feeling of home without risking their safety. Due to the independence and preservation of dignity that these environments support, "dementia villages" may also promote physical activity. The physical activity comes from the residents' ability to attend programs that are of interest and freedom to walk about the village [32, 33].

## 5. Conclusions

While few studies proved physical activity has a significant role in overall QOL, there were several studies that demonstrated how an intervention involving physical activity improved aspects of QOL. Overall, these study findings point toward a positive relationship between physical activity and QOL among individuals with dementia. Large controlled trials among both nursing home and community dwelling study participants are needed to provide the evidence base for intervention program development. One study reported evidence that social interaction may be critical to improving QOL in dementia patients, but this line of research was outside the scope of this current review. Study interventions involving physical activity or social interaction alone, and in combination, could help identify optimal program interventions among this growing population.

## Author Contributions

TPD and NLS developed the topic of this review and the search terms. TPD screened abstracts, created tables, and drafted the manuscript. TPD, NLS, and EBO interpreted tables and edited the manuscript.

## Competing Interests

The authors have declared that no competing interests exist.

## References

1. Hebert L, Weuve J, Scherr P, Evans D. Alzheimer disease in the United States (2010-2050) estimated using the 2010 Census. Neurology. 2013; 80: 1778-1783.
2. Alzheimer's Association. 2019 Alzheimer's disease facts and figures. Alzheimers Dement. 2019; 3: 321-387. doi: 10.1016/j.jalz.2019.01.010.
3. Genworth's 15th annual cost of care survey shows continuing rise in long term care costs. New York: Genworth; 2019. Available from: https://newsroom.genworth.com/2018-10-16-Genworths-15th-Annual-Cost-of-Care-Survey-Shows-Continuing-Rise-in-Long-Term-Care-Costs.
4. Genworth 2017 annual cost of care survey: Costs continue to rise across all care settings. New York: Genworth; 2017. Available from: http://investor.genworth.com/investors/news-releases/archive/archive/2017/Genworth-2017-Annual-Cost-of-Care-Survey-Costs-Continue-to-Rise-Across-All-Care-Settings/default.aspx.
5. Vickrey B, Mittman B, Connor K, Pearson M, Della Penna R, Ganiats T. The effect of a disease management intervention on quality and outcomes of dementia care: A randomized, controlled trial. Ann Intern Med. 2006; 145: 713-726.

6. Kemoun G, Thibaud M, Roumagne N, Carette P, Albinet C, Toussaint L, et al. Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dement Geriatr Cogn Disord. 2010; 29: 109-114.
7. Steinberg M, Leoutsakos JS, Podewils LJ, Lyketsos CG. Evaluation of a home-based exercise program in the treatment of Alzheimer's disease: The maximizing independence in dementia (MIND) study. Int J Geriatr Psychiatry. 2009; 24: 680-685.
8. Jadad AR, Moore RA, Carroll D, Jenkinson C, J Reynolds D, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials. 1996; 17: 1-12.
9. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (Minors): Development and validation of a new instrument. ANZ J Surg. 2003; 73: 712-716.
10. Lamb SE, Sheehan B, Atherton N, Nichols V, Collins H, Mistry D, et al. Dementia and Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: Randomised controlled trial. BMJ. 2018; 361: k1675. doi: 10.1136/bmj.k1675.
11. Ballard C, Orrell M, Sun Y, Moniz-Cook E, Stafford J, Whitaker R, et al. Impact of antipsychotic review and non-pharmacological intervention on health-related quality of life in people with dementia living in care homes: WHELD-a factorial cluster randomised controlled trial. Int J Geriatr Psychiatry. 2016; 32: 1094-1103.
12. Henskens M, Nauta I, Drost K, Scherder E. The effects of movement stimulation on activities of daily living performance and quality of life in nursing home residents with dementia: A randomized controlled trial. Clin Interv Aging. 2018; 13: 805-817.
13. Hoffmann K, Høgh P, Johannsen P, Beyer N, Vogel A, Vestergaard K, et al. Moderate-to-High intensity physical exercise in patients with Alzheimer's disease: A randomized controlled trial. J Alzheimer's Dis. 2016; 50: 443-453.
14. Telenius EW, Engedal K, Bergland A. Effect of a high-intensity exercise program on physical function and mental health in nursing home residents with dementia: An assessor blinded randomized controlled trial. PLoS One. 2015; 10: e0126102. doi: 10.1371/journal.pone.0126102.
15. Tanaka S, Yamaguchi H, Honda S, Araya K, Sato Y, Nakano H. Comparison between group and personal rehabilitation for dementia in a geriatric health service facility: Single-blinded randomized controlled study. Psychogeriatrics. 2016; 17: 177-185.
16. Ettema TP, Dröes R-M, de Lange J, Mellenbergh GJ, Ribbe MW. QUALIDEM: Development and evaluation of a dementia specific quality of life instrument—validation. Int J Geriatr Psychiatry. 2007; 22: 424-430.
17. Ettema TP, Dröes R-M, de Lange J, Mellenbergh GJ, Ribbe MW. QUALIDEM: Development and evaluation of a dementia specific quality of life instrument. Scalability, reliability and internal structure. Int J Geriatr Psychiatry. 2007; 22: 549-556.
18. Weiner MF, Martin-Cook K, Svetlik DA, Saine K, Foster B, Fontaine CS. The quality of life in late-stage dementia (QUALID) scale. J Am Med Dir Assoc. 2000; 1: 114-116.
19. Terada S, Ishizu H, Fujisawa Y, Fujita D, Yokota O, Nakashima H, et al. Development and evaluation of a health-related quality of life questionnaire for the elderly with dementia in Japan. Int J Geriatr Psychiatry. 2002; 17: 851-858.

20. Mulhern B, Rowen D, Brazier J, Smith S, Romeo R, Tait R, et al. Development of DEMQOL-U and DEMQOL-PROXY-U: Generation of preference-based indices from DEMQOL and DEMQOL-PROXY for use in economic evaluation. Health Technol Assess. 2013; 17: 1-160.
21. Ware JE. SF-36 health survey update. Spine Phila Pa 1976. 2000: 25: 3130-3139.
22. Logsdon RP, Gibbons LP, McCurry SP, Teri LP. Assessing quality of life in older adults with cognitive impairment. Psychosom Med. 2002; 64: 510-519.
23. EuroQol. About EQ-5D. https://euroqol.org/eq-5d-instruments/
24. Smith SC, Lamping DL, Banerjee S, Harwood RH, Foley B, Smith P, et al. Development of a new measure of health-related quality of life for people with dementia: DEMQOL. Psychol Med. 2007; 37: 737-746.
25. La Rue A, Felten K, Turkstra L. Intervention of multi-modal activities for older adults with dementia translation to rural communities. Am J Alzheimers Dis Other Demen. 2015; 30: 468-477.
26. Henskens M, Nauta IM, Scherder EA, Oosterveld FJ, Vrijkotte S. Implementation and effects of movement-oriented restorative care in a nursing home-a quasi-experimental study. BMC Geriatr. 2017; 17: 243. doi: 10.1186/s12877-017-0642-x.
27. Taylor ME, Lord SR, Brodaty H, Kurrle SE, Hamilton S, Ramsay E, et al. A home-based, carer-enhanced exercise program improves balance and falls efficacy in community-dwelling older people with dementia. Int Psychogeriatrics. 2017; 29: 81-91.
28. Olsen C, Pedersen I, Bergland A, Enders-Slegers M, Jøranson N, Calogiuri G, et al. Differences in quality of life in home-dwelling persons and nursing home residents with dementia-a cross-sectional study. BMC Geriatr. 2016; 16: 137. doi: 10.1186/s12877-016-0312-4.
29. Morris JC. The clinical dementia rating (CDR): Current version and scoring rules. Neurology. 1993; 43: 2412-2414.
30. Paw CA, de Jong N, Schouten EG, van Staveren WA, Kok FJ. Physical exercise or micronutrient supplementation for the wellbeing of the frail elderly? A randomised controlled trial. Br J Sports Med. 2002; 36: 126-131.
31. Bunn F, Burn AM, Goodman C, Robinson L, Rait G, Nortonet S, et al. Comorbidity and dementia: A mixed-method study on improving health care for people with dementia (CoDem). Heal Serv Deliv Res. 2016; 4: 1-156.
32. New residents settle into “dementia village” in Langley. Toronto: CBC News; 2019. Available from: https://www.cbc.ca/news/canada/british-columbia/dementia-village-langley-1.5267630.
33. Planos J. The dutch village where everyone has dementia. Washington: The Atlantic; 2014. Available from: https://www.theatlantic.com/health/archive/2014/11/the-dutch-village-where-everyone-has-dementia/382195/.


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Editorial

# Immune Senescence and Covid-19 Pandemic

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**Abstract**

Covid-19 pandemic has been infecting a substantial portion of the world population, thereby revealing quality deficits in health care in the majority of the countries around the globe. Severe illness and mortality from Covid-19 infection are present predominantly in minorities; especially they are more frequent in geriatric patients. Unfortunately, our knowledge is limited about what accounts for the variability in immune response from one person to another. This question is far from being merely academic, and finding its answer assumes critical importance for the future of global health.

**Keywords**

Covid-19; immune senescence; elderly; ACE2; hypertension

Risk factors, such as smoking, physical inactivity, obesity, and inappropriate eating habits, are significantly influenced by the environment in which people live. Social factors, especially in minority populations, also contribute to a disproportionately high rate of chronic illness and delays in getting health care [1]. In some countries, especially in low-income and education minorities, these factors could explain the high frequency and virulence of Covid-19 infection. Climate changes could put an additional one billion people at risk of tropical vector-borne diseases, which are emerging with increasing frequency and have the potential for causing pandemic diseases [1].

However, the highest mortality from Covid-19 infection is observed mostly in geriatric patients. This fact should force medical science to understand and determine global demographic changes; the world is facing. According to the United Nations projections, by 2050, there will be more than twice as many people over 65 as there are children under 5, and the number of people older than 65 globally will surpass the number of people in the age group of 15-24 years [2]. This global aging might pose widespread public health challenges, significantly increasing the burden of geriatric pathologies and exposing the vulnerable elderly population to infectious diseases [1].

Angiotensin-converting enzyme-2 (ACE2) is the receptor for SARS-Cov-2 virus. It has been suggested the differential levels of ACE2 in the cardiac and pulmonary tissues of younger versus geriatric patients might be partially responsible for the viral virulence observed among the patients. Indeed, the use of renin-angiotensin system blockers in patients with Covid-19 infection has been much debated, and it has been concluded that these blockers should not be withdrawn [3-5]. Unfortunately, it remains undetermined whether the Covid-19 mortality risks in geriatric patients can be interpreted by analyzing data of younger patients alone. Undoubtedly, health conditions associated with aging, especially cardiovascular diseases, cancers, metabolic and autoimmune diseases, and the treatments for these pathologies, interfere with the SARS-Cov-2 virus infection. Also, immune senescence, i.e., a progressive age-related decline of innate and adaptive immune responses, substantially and adversely affects the responses to infectious diseases and vaccines. Indeed, the Shingrix vaccine for shingles has proven very effective in people over 70, but our understanding of how to generate effective immunity in the elderly remains poor, and several studies have shown that vaccine efficacy decreases significantly with advancing age [6].

Protecting geriatric patients will be central, but even the most efficient health systems cannot properly cope with these individuals/issues. Despite decades of standardized measurements, public reporting, and control programs, the average quality performance of health care remains insufficient. Indeed, in the USA, adults receive about 55% of recommended care for the leading causes of diseases and death [7]. These figures almost match with those in most countries. A good example is the management of arterial hypertension, a very common and treatable chronic pathology - a major contributor to morbidity and mortality. In the USA, in 2017 hypertension (HTN) accounted for 23 deaths per million population, but in Non-Caucasian patients, HTN rates were significantly higher, e.g., in Afro-Americans, 54.1 deaths per 1000,000 men and 37.8 per 100,000 women were recorded [8].

Clinicians know that good therapy requires applying the most effective treatment that increases better outcomes. This approach should be customized to the specific preferences and health needs of the individuals, detecting and diagnosing the pathologies, choosing the right treatment, ensuring adherence, checking treatment effectiveness, and adjusting appropriate therapy. Maintaining professionalism is crucial, although insufficient cornerstone of high-quality care and, in reality, quality of care is rarely about good health professionals versus bad ones. However, it is difficult to get a good quality of care without supportive protocols, tools and teamwork. To improve and streamline high-quality health care, an enduring framework for evaluating process, structures, and outcomes was propounded [9]. In recent time, policymakers emphasized three additional levers to improve the quality of health care: measurements, incentives, and social factors [10]. On the other hand, the relationship between politicians, policymakers, and physicians remains unhealthy [11, 12].

To conclude, this paper underlines the need that due to global demographic changes, the Covid-19 pandemic should force medical science to understand whether the immune system of geriatric patients is adequate to be properly treated with vaccines.

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Mrs. Jacqueline Bugmann typed the manuscript.

**Author Contributions**

The author did all the research work of this study.

**Competing Interests**

The author has declared that no competing interests exist.

**References**

1. Koff WC, Williams MA. Covid-19 and immunity in aging populations – A new research agenda. New Engl J Med. 2020; 383: 804-805.
2. World population prospects 2019. New York: United Nations; 2019. Available from: https://population.un.org/wwp/.
3. Bavishi C, Maddox TM, Messerli FH. Coronavirus disease (COVID-19) infection and renin angiotensin system blockers. JAMA Cardiol. 2020; 5: 745-747.
4. Pesheva E. Coronavirus and the heart. Health & Medicine. Cambridge, MA: Harvard Gazette; 2020. Available from: https://news.harvard.edu/gazette/story/2020/04/covid-19s-consequences-for-the-heart/.
5. Eberli F. COVID-19 und das Herzgefäss-System. Erlenbach: Medinfo aerzteverlag; 2020. Available from: https://www.medinfo-verlag.ch/covid-19-und-das-herzgefaess-system/.
6. Poland GA, Ovsyannikova IG, Kennedy RB. Personalized vaccinology: A review. Vaccine. 2018; 36: 5350-5357.
7. Centers for disease Control and prevention. Antibiotic resistance threats in the United States, 2013. Atlanta, GA: US Department of Health and Human Services; 2015. Available from: https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.
8. Presidential Advisory Council on Combating Antibiotic-Resistant bacteria: 2020-2025. A report with recommendations. Washington, D. C.: Assistant Secretary for Health; 2019. Available from: https://www.hhs.gov/sites/default/files/PACCARB%20NAP%20Report%20FINAL%20Approved%20by%20Council.pdf.
9. Burnham JP, Olsen MA, Kollef MH. Re-estimating annual death due to multidrug-resistant organism infections. Infect Control Hosp Epidemiol. 2019; 40: 112-113.
10. McGlynn EA. Improving the quality of US Health Care – What will it take? New Engl J Med. 2020; 383: 801-803.
11. Cocco G. Bureaucracy and medicine, an unholy Marriage. Cardiovasc Med. 2012; 15: 243-244.
12. Cocco G. Physcians' dissatisfaction: A short review. Heart Mind. 2019; 2: 35-39.


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Research Article

# Parkinson's Disease Motor and Non-Motor Features Accompanying Insomnia and Excessive Daytime Sleepiness Symptoms, a Large Population-Based Study

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**Abstract**

Insomnia and excessive daytime sleepiness are the most common sleep disturbances in Parkinson's disease. This study aims at better understanding how severity of PD motor and non-motor features and dopaminergic treatments contribute to these sleep symptoms in the first decade of PD. Data from a community-based cohort of PD patients was used to model cross-sectional PD-related risk factors for insomnia and EDS sleep scores using linear regression models adjusted for age, gender, and PD duration. Longitudinal changes in sleep scores were assessed with paired t-tests. For 481 patients who completed the MOS-Sleep

questionnaire at least once, high levodopa daily doses (500mg+) and severe autonomic and complex non-motor symptoms (depression, anxiety, apathy, hallucinations and dopamine dysregulation syndrome) were associated with both EDS and insomnia symptoms. Higher total motor UPDRS and especially tremor sub-scores and motor complications were associated only with insomnia, while axial/posture/gait and body bradykinesia UPDRS sub-scores were associated only with EDS. In 156 patients, with a second sleep measure on average after 2.2 years of follow-up, only EDS scores increased over time. Groups defined by worse PD features severity at first follow-up (UPDRS 35+, PD duration 6.5+ years, or LED 500mg+) had larger average increases in EDS score over time. These findings provide evidence that motor and non-motor dysfunction in PD are associated with insomnia and EDS symptoms, but specific features and level of severity affect sleep symptoms differently. Motor manifestations related to tremor and dyskinesia are associated with sleep quantity and quality, measured by insomnia symptoms, while axial motor features are related to EDS symptoms.

**Keywords**
Parkinson's disease; motor symptoms; non-motor symptoms; sleep problems; circadian dysfunction; insomnia; excessive daytime sleepiness

## 1. Introduction

Sleep disturbances have been increasingly recognized as important non-motor components of the Parkinson's disease (PD) syndrome [1-5]. The most frequent sleep or sleep-related problems that patients report are excessive daytime sleepiness (EDS), insomnia and REM sleep behavior disorder (RBD) [6]. Insomnia and EDS are sleep-wake disturbances that may indicate disruption of the circadian rhythm as part of the neurodegenerative process characteristic of PD [7, 8].

Insomnia is the difficulty to initiate or maintain sleep and, when it manifests chronically, insomnia has well-known negative consequences for health and quality of life [9, 10]. While PD patients usually do not have trouble initiating sleep, insomnia manifests mainly as the difficulty to maintain sleep, resulting in sleep fragmentation and early awakening [11]. EDS refers to a subjective complaint characterized by difficulty in remaining awake during the day, usually accompanied by sleep initiation if the person stays inactive [12], and it is more common in PD patients than in the general population [13]. EDS can be secondary to other sleep disorders and health factors, or can be attributable to primary central disorders of hypersomnolence, as defined in the International Classification of Sleep Disorders (ICSD) [14].

Better insight into what causes sleep problems in PD will encourage improvements in clinical care and quality of life of patients. In the last decade, a number of studies suggested the following risk factors for insomnia and/or EDS in PD [15-24]: PD duration, motor disability, dopaminergic medications, depression and anxiety, and autonomic symptoms. However, these studies mainly enrolled patients from tertiary clinics or, when community-based, they were conducted in European countries or had a small number of participants. Also, they yielded conflicting results as to which PD-related clinical symptoms are related to sleep disorders. Previously, data from a large

community-based cohort of PD patients was analyzed to investigate the role of REM sleep behavior disorder on PD progression [25]. Relying on the same cohort of PD patients, the present study assesses contributions of severity of PD motor and non-motor features and treatment with levodopa to insomnia and EDS symptoms in patients who are, on average, within six years (range: 2 - 15) of an initial PD diagnosis.

## 2. Methods

### *2.1 Study Design*

The Parkinson's Environment and Genes Study (PEG), identified new-onset (up to 5 years after diagnosis) PD cases at baseline from 2001 to 2007 (PEG 1), and from 2011 to 2017 (PEG 2), from the entire population of three California counties [26]. PEG 1&2 participants were seen for a first follow-up, on average 3.2 years after their baseline visit. PEG 1 participants were additionally seen a second time, on average 2.2 (±0.5) years later. At all time points, participants were examined at a local clinic by PEG study movement disorders specialists, who confirmed the diagnosis according to common criteria [26], and evaluated motor signs and symptoms, preferably with patients "off" PD medications.

The UCLA Institutional Review Board approved all phases of the study protocol, and participants were informed of all procedures and their rights and provided written informed consent.

### *2.2 Data Collected*

Study neurologists examined patients and scored motor disability using the Unified Parkinson's Disease Rating Scale (UPDRS, and later MDS-UPDRS), parts III and IV and Hoehn and Yahr staging (HY). The exams were preferably conducted with patients "off" PD medications (>90% of exams were "off"). UPDRS-III scores were corrected for missing items that cannot be evaluated (such as arising from chair in paraplegic patients), and when only an "on medication" exam was possible, as previously described [27]. PD motor subtypes of Postural Imbalance and Gait Dysfunction (PIGD), Tremor Dominant (TD), or indeterminate were calculated as ratios of UPDRS-III sub-scores, as described previously [28]. PD medication information, including levodopa and dopamine agonist use, were summarized into a daily levodopa equivalent dose (LED) [29].

During all visits, trained research assistants interviewed participants to collect demographic, lifestyle, and medical history information, including current PD medication use and dosage. We calculated UPDRS-III motor total score and sub-scores; the latter by summing specific items corresponding to total tremor [30] (rest and postural), rigidity, limb bradykinesia [31] (fingers tapping, hands grip, hands rapid movements, leg agility), and axial/posture/gait [31] (speech, facial expression, arise from chair, posture, postural stability, gait, and body bradykinesia).

Additional standardized instruments were adopted only during follow-up, including those measuring insomnia and EDS, as well as the UPDRS-IA, IB and II to assess non-motor and motor impacts of PD on experiences of daily living. We rely on the Sleep Survey of the Medical Outcomes Study (MOS-Sleep) for recording symptoms of insomnia and EDS. It contains twelve items, each with six answer options on a Likert scale, measuring subjective experiences of sleep in the past four weeks across several domains including sleep initiation, maintenance, quantity/duration,

perceived adequacy, respiratory problems and somnolence. The MOS-Sleep has been validated and been used to study chronic diseases; its content is very comparable to two questionnaires widely used in PD sleep research, the Pittsburgh Sleep Quality Index (PSQI) and the Parkinson's Disease Sleep Scale (PDSS) [32].

MOS-Sleep items are summarized to create five scores (sleep disturbance, somnolence, sleep adequacy, snoring, and shortness of breath during sleep) ranging from 0 to 100, with higher scores indicating worse sleep quality, except for the adequacy score, which is reversed. For this study's purposes, we adopted the continuous scores (0 to 100) for sleep disturbance (items: having trouble falling asleep, how long to fall asleep, sleep was not quiet, awake during sleep time, and having trouble falling asleep again) as a measure of insomnia symptoms, and for somnolence (items: drowsy during day, having trouble staying awake during the day, taking naps), as a measure of EDS symptoms.

### *2.3 Statistical Analysis*

Analyses were conducted in statistical software SAS (SAS 9.4, SAS Institute, Cary, NC), figures were generated in R. Insomnia and EDS scores were normally distributed univariately and across risk factors of interest; such as gender, age and PD duration at the time sleep measures.

Sleep scores were z-standardized, centering on mean 0 and standard deviation 1. First, mean crude z-standardized MOS-Sleep scores by patients' characteristics were estimated. To visualize how PD-related factors (PD duration, age at diagnosis, UPDRS-III, UPDRS-IA, and LED) may influence sleep symptoms, crude z-standardized insomnia and EDS scores were plotted according to these PD-related factors, stratifying by gender, and generating Pearson correlation coefficients.

Adjusted mean differences in sleep scores between binary measures of PD severity were modeled using linear regressions (implemented with maximum likelihood in Proc Genmod; SAS 9.4) including potential confounders as covariates; i.e., at a minimum we included gender, age at interview, and PD duration. PD measures were dichotomized, i.e., at the median for PD duration (6.5 years) at first sleep assessment; at 35 points for the UPDRS-III motor; at 500 mg for the LED as proposed previously [17]; for the UPDRS-II (20 points), UPDRS-IA (5 points), and the autonomic symptoms score (8 points) the cut-points correspond to the respective $75^{th}$ percentile of the score. To estimate associations between UPDRS motor sub-scores with insomnia and EDS scores, similar adjusted linear regression models were used, but continuous motor sub-scores were also z-standardized and results presented as β-coefficients. In sensitivity analyses, additional potential confounders were included guided by mechanisms proposed and depicted in Directed Acyclic Graphs [33] (Supplemental Figure S1) as detailed in Results.

In a subset of the PEG1 cohort with information on sleep measures (n=156) at an additional follow-up time, average sleep scores at both follow-up times stratified by PD severity measures were compared using t-tests as well as paired t-tests to identify differences in average sleep scores over time by PD-severity at first follow-up (between and within groups).

## 3. Results

This study included 481 PD patients who completed the MOS-Sleep at least once, of whom 459 (95%) also completed a simultaneous motor examination. The majority was male (62%), White (77%), assessed for sleep quality on average 6.3 ± 3.0 years after their first PD diagnosis, and 69%

exhibited a PIGD motor phenotype (Table 1). Among the sleep domains the MOS assesses, EDS received the highest absolute score, on a scale from 0 to 100 (mean 42.4 ± SD 23.7), followed by snoring (34.5 ± 33.4) and insomnia (30.5 ± 22.6). Insomnia and EDS measures were moderately positively correlated (ρ=0.34) (Supplemental Figure S2). Figure 1 shows linear correlations of MOS-Sleep scores with PD-related measures; patients diagnosed at younger ages and with longer PD duration had worse insomnia symptom scores, but these PD features were not correlated with EDS (Figure 1). All other PD-related measures were positively correlated with both insomnia and EDS, in men and women.

Table 2 presents cross-sectional mean differences in insomnia and EDS scores comparing groups defined by PD severity, adjusting for gender, age and PD duration. In these models, a PD duration of 6.5+ years was associated with higher EDS, but not insomnia. Conversely, a UPDRS-III motor total score of 35+ and the presence of motor complications were associated with higher average insomnia scores, but not with EDS. Specifically, off-dystonia and motor fluctuations were the motor complications associated with worse insomnia scores. Estimates for motor complications remained unchanged in models further adjusted for levodopa use or dose, and for UPDRS-III scores. Likewise, the strong positive associations of non-motor (UPDRS-IA) and autonomic symptoms with insomnia and EDS scores persisted when the models were further adjusted for UPDRS-III or levodopa dose.

Only few patients did not take PD medications (8%) or solely used dopamine agonists (6%), while 54% were treated with levodopa only, and 32% with a combination of levodopa and dopamine agonists (Table 1). Patients with LED ≥500mg had worse insomnia and EDS symptoms, compared to the group with <500mg, while higher doses of dopamine agonists (≥200mg vs. <200mg) did not significantly impact the sleep scores. These estimates remained unchanged in models that included the motor UPDRS-III scores, or axial/postural/gait or tremor sub-scores (results not shown).

**Table 1** Distribution of demographics, PD-related characteristics and MOS-Sleep scale scores for Insomnia and EDS, at first follow-up.

| | | **N (%)** | **Crude Mean Standardized MOS-Sleep score** | |
|---|---|---|---|---|
| | | | Insomnia (Mean ± SD) | EDS (Mean ± SD) |
| Total | | 481 (100) | 0 ± 1 | 0 ± 1 |
| Study cohort[1] | PEG 1 | 234 (49) | -0.051 ± 0.978 | 0.034 ± 0.978 |
| | PEG 2 | 247 (51) | 0.049 ± 1.020 | -0.033 ± 1.022 |
| Age at interview | 65 or less | 119 (25) | 0.299 ± 1.139 | 0.040 ± 1.026 |
| | 66 to 80 | 263 (55) | -0.107 ± 0.895 | -0.013 ± 0.937 |
| | more than 80 | 95 (20) | -0.078 ± 1.026 | -0.013 ± 1.136 |
| Gender | women | 183 (38) | 0.002 ± 0.993 | -0.226 ± 0.942 |
| | men | 298 (62) | -0.001 ± 1.006 | 0.141 ± 1.010 |
| Ethnicity | White | 371 (77) | -0.057 ± 0.959 | 0 ± 0.985 |
| | Latino | 79 (17) | 0.183 ± 1.112 | -0.059 ± 1.060 |
| | Other | 29 (6) | 0.228 ± 1.124 | 0.160 ± 1.043 |
| Education | <12 years | 71 (15) | 0.259 ± 1.097 | -0.037 ± 1.064 |

| | | | | |
|---|---|---|---|---|
| | 12+ | 411 (85) | -0.045 ± 0.978 | 0.009 ± 0.989 |
| Age at PD diagnosis | ≤60 | 131 (27) | 0.284 ± 1.136 | 0.089 ± 1.034 |
| | >60 | 350 (73) | -0.104 ± 0.925 | -0.033 ± 0.987 |
| Age at PD duration | ≤6.5 years | 279 (58) | -0.120 ± 0.906 | -0.131 ± 0.948 |
| | >6.5 years | 202 (42) | 0.168 ± 1.099 | 0.183 ± 1.043 |
| Motor subtype (missing=27) | tremor dominant or indeterminate | 151 (33) | -0.032 ± 0.939 | -0.074 ± 0.969 |
| | PIGD | 303 (67) | 0.030 ± 1.025 | 0.035 ± 0.990 |
| UPDRS-III[2] total score | <35 (missing= 22) | 349 (76) | -0.054 ± 0.957 | -0.041 ± 0.951 |
| | 35+ | 110 (24) | 0.235 ± 1.107 | 0.146 ± 1.082 |
| Hoehn and Yahr | stages 0-2.5 (missing= 33) | 330 (74) | -0.011 ± 0.973 | -0.063 ± 0.957 |
| | stage 3+ | 118 (26) | -0.025 ± 1.054 | 0.105 ± 0.991 |
| LED[3] Dopamine agonists only, 200 mg+ | | 114 (25) | 0.036 ± 1.001 | 0.009 ± 0.929 |
| LED[3] Levodopa only, 500 mg+ | | 188 (40) | 0.164 ± 1.064 | 0.240 ± 1.046 |
| LED[3] total, 600 mg+ | | 197 (42) | 0.154 ± 1.063 | 0.146 ± 1.039 |
| UPDRS-IV[4] (motor complications) any present (missing= 22) | | 235 (53) | 0.200 ± 1.051 | 0.041 ± 0.923 |
| UPDRS-IV sub-scores | Dyskinesia, present[5] | 97 (22) | 0.259 ± 1.027 | 0.031 ± 0.896 |
| | Motor Fluctuations, present | 190 (43) | 0.223 ± 1.036 | 0.015 ± 0.941 |
| | Off-Dystonia, present | 77 (17) | 0.380 ± 1.119 | 0.183 ± 0.956 |
| UPDRS-II[6] (motor ADL) | score, 20+ | 140 (32) | 0.269 ± 1.092 | 0.305 ± 1.011 |
| | score 5+ | 114 (25) | 0.450 ± 1.121 | 0.359 ± 0.974 |
| UPDRS-IA (non-motor, complex behaviours)[7] | Autonomic sympoms[8], score 8+ | 118 (25) | 0.177 ± 1.051 | 0.331 ± 0.959 |
| | Urinary problems, present | 350 (74) | 0.070 ± 1.013 | 0.100 ± 0.999 |

1. PEG=Parkinson's Environment and Genes.

2. UPDRS-III (rated by physician), motor signs: speech, facial expression, tremor at rest (face, hands, feet) amplitude and constancy, rigidity (neck, arms, legs), fingers and toes tapping, hand grip and movements, leg agility, arising from chair, posture, gait and freezing of gait, postural stability, body bradykinesia, postural and kinetic tremor.

3. LED: Levodopa Equivalent Daily Dose.

4. UPDRS-IV (applied by physician), motor complications items: dyskinesias (time spent and functional impact), motor fluctuations (time spent in off-state, functional impact and complexity of fluctuations), painful off-state present and time spent.

5. Presence of dyskinesia: measured by UPDRS-IV question "Time Spent with Dyskinesias", where option "0=Normal" corresponds to "No Dyskinesia" and any other option (1,2,3 or 4) corresponds to "Yes Dyskinesia".

6. UPDRS-II: Motor Aspects of Experiences of Daily Living (self-completed) items: speech, saliva/drooling, chewing/swallowing, eating, dressing, hygiene, handwriting, hobbies, turning in bed, tremor, getting off bed/car/chair, walking/balance, freezing.

7. UPDRS-I: Non-Motor Aspects of Experiences of Daily Living.

8. UPDRS-IA (rated by physician), complex behaviours items: cognitive impairment, hallucinations, depressed mood, anxious mood, apathy, features of dopamine dysregulation syndrome.

9. Autonomic symptoms score: constipation, urinary, light headedness, saliva/drooling, chewing/swallowing.

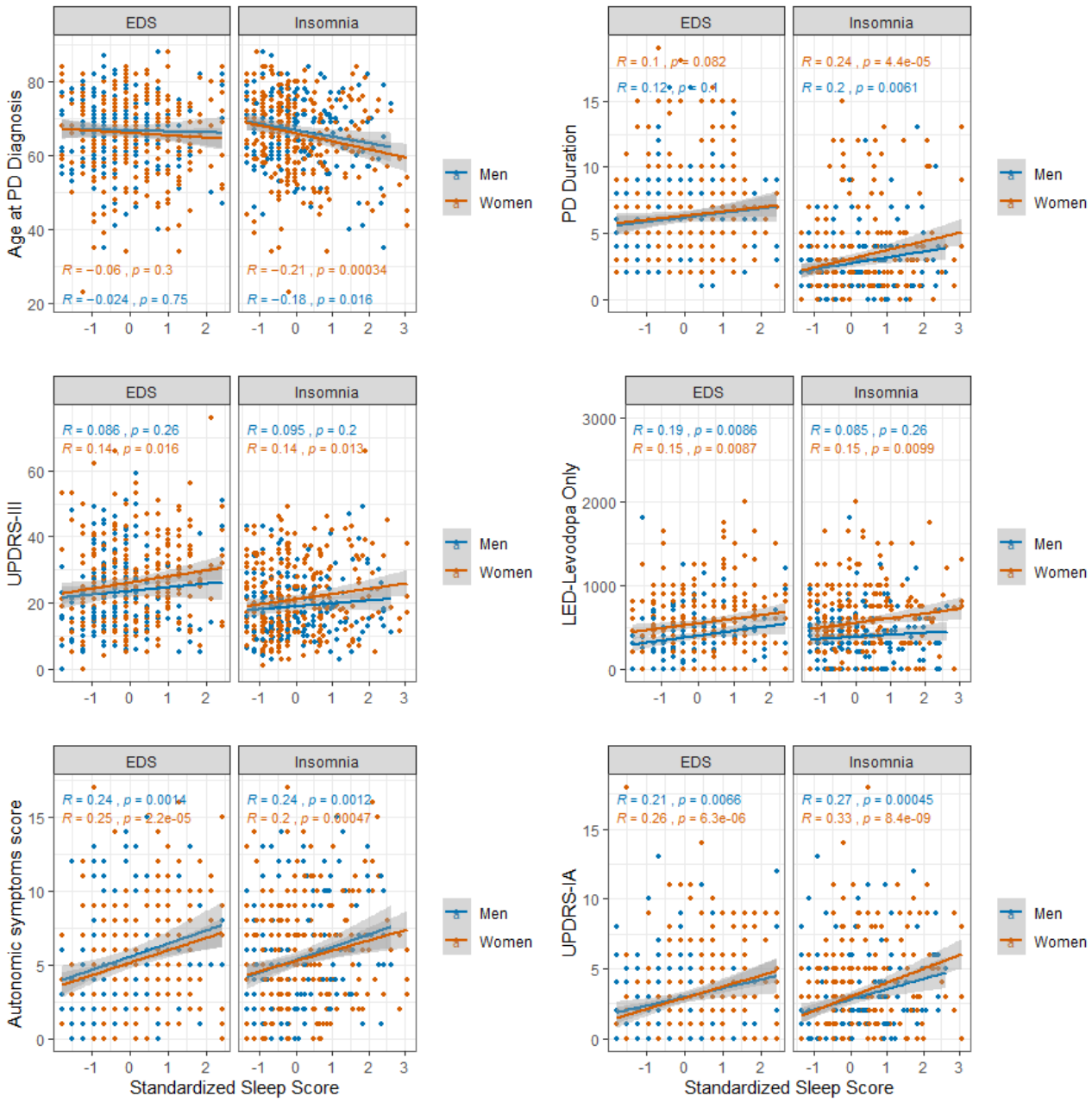


**Figure 1** Scatterplot of standardized sleep scores (mean 0, SD 1) by PD characteristics stratified by gender. Including best fit linear correlation line, Pearson correlation coefficients, and p-values. N=481 (except for UPDRS-III, N=459).

**Table 2** Linear regressions of insomnia and EDS scores on PD-related characteristics (**cross-sectional**), adjusted for gender, age and duration of Parkinson's disease in years, N=459.

| PD severity measures (binary) | Insomnia | EDS |
|---|---|---|
| | Mean difference[1] (95% CI) | |
| PD duration[2], years, 6.5+ vs. < 6.5 | 0.02 (-0.26, 0.29) | 0.34 (0.06, 0.62) |
| UPDRS-III[3] total score, 35+ vs. < 35 | 0.27 (0.06, 0.49) | 0.14 (-0.07, 0.35) |
| HY, stage 3+ vs. stage< 3 (Total N= 448) | 0.08 (-0.13, 0.29) | 0.19 (-0.02, 0.40) |
| Motor subtype, PIGD[4] vs. other | 0.12 (-0.07, 0.32) | 0.14 (-0.05, 0.33) |
| LED[5], Levodopa only, 500mg+ vs. <500mg | 0.22 (0.03, 0.41) | 0.29 (0.10, 0.47) |
| Only dopamine agonists, 200mg+ vs. <200mg | -0.10 (-0.32, 0.11) | -0.05 (-0.26, 0.17) |
| Total, Levodopa and dopamine agonists, 600mg+ vs. <600mg | 0.17 (-0.02, 0.35) | 0.15 (-0.04, 0.34) |
| UPDRS-IV[6] total (motor complications), any present vs. not | 0.25 (0.06, 0.44) | 0.04 (-0.15, 0.23) |
| UPDRS-IV, Dyskinesia[7], present vs. not | 0.13 (-0.10, 0.36) | -0.04 (-0.27, 0.19) |
| Motor Fluctuations, present vs. not | 0.24 (0.05, 0.43) | -0.02 (-0.20, 0.17) |
| Off-Dystonia, present vs. not | 0.33 (0.09, 0.58) | 0.23 (-0.01, 0.47) |
| UPDRS-II[8] score, 20+ vs. <20 | 0.37 (0.18, 0.57) | 0.40 (0.20, 0.60) |
| UPDRS-IA[9] score, 8+ vs. <8 | 0.54 (0.34, 0.74) | 0.45 (0.25, 0.65) |
| Autonomic symptoms[10] score, 5+ vs. < 5 | 0.27 (0.06, 0.48) | 0.43 (0.23, 0.64) |
| Urinary problems, present vs. not | 0.27 (0.07, 0.47) | 0.32 (0.12, 0.52) |

1. Adjusted for gender, age, and duration of PD.

2. Adjusted for gender and age.

3. UPDRS-III (rated by physician), motor signs: speech, facial expression, tremor at rest (face, hands, feet) amplitude and constancy, rigidity (neck, arms, legs), fingers and toes tapping, hand grip and movements, leg agility, arising from chair, posture, gait and freezing of gait, postural stability, body bradykinesia, postural and kinetic tremor.

4. Postural Instability and Gait Disturbance (or Dysfunction, Difficulty)

5. LED: Levodopa Equivalent Daily Dose

6. UPDRS-IV (applied by physician), motor complications items: dyskinesias (time spent and functional impact), motor fluctuations (time spent in off-state, functional impact and complexity of fluctuations), painful off-state present and time spent.

7. Presence of dyskinesia: measured by UPDRS part IV question "Time spent with dyskinesias", where option "0=Normal" corresponds to "no dyskinesia" and any other option (1,2,3 or 4) corresponds to "yes Dyskinesia"

8. UPDRS-II (self-completed), motor aspects of experiences of daily living items: speech, saliva/drooling, chewing/swallowing, eating, dressing, hygiene, handwriting, hobbies, turning in bed, tremor, getting off bed/car/chair, walking/balance, freezing.

9. UPDRS-IA (rated by physician), complex behaviors items: cognitive impairment, hallucinations, depressed mood, anxious mood, apathy, features of dopamine dysregulation syndrome.

10. Autonomic symptoms score: constipation, urinary, light headedness, saliva/drooling, chewing/swallowing**.**

Table 3 shows adjusted linear associations of UPDRS-III motor sub-scores with insomnia and EDS. Total tremor and limb bradykinesia were positively associated only with worse insomnia, while axial/postural/gait was associated only with EDS scores, however, these associations were greatly attenuated in models adjusted for (levodopa-only) LED (results not shown). The association of the body bradykinesia sub-score with EDS persisted after adjustment for LED, but was greatly reduced after adjustment for the geriatric depression scale (GDS) score (β= 0.06; 95% CI: -0.03, 0.15).

**Table 3** Linear regressions of insomnia and EDS scores on UPRDS-III motor sub-scores (**cross-sectional**), adjusted for gender, age and duration of Parkinson's disease in years. Sleep scores and motor sub-scores are z-standardized, N=459.

| **UPDRS-III motor sub-scores, per 1 SD increase** | **Insomnia** **β Coefficient (95% CI)** | **EDS** **β Coefficient (95% CI)** |
|---|---|---|
| Total tremor | 0.09 (0.00, 0.18) | 0.04 (-0.05, 0.13) |
| Limb bradykinesia | 0.11 (0.02, 0.21) | 0.06 (-0.03, 0.15) |
| Rigidity | 0.05 (-0.04, 0.15) | -0.01 (-0.11, 0.08) |
| Axial, posture and gait | 0.07 (-0.03, 0.17) | 0.10 (0.00, 0.20) |
| Body bradykinesia | -0.01 (-0.10, 0.09) | 0.10 (0.01, 0.19) |

Longitudinal information on insomnia and EDS scores was available for 156 participants from the PEG1 study cohort at a second follow-up, on average 2.2 ± 0.5 years after the first, and an average PD duration of 7.4 ± 2.5 years (for the PEG2 cohort a second follow-up has not yet been completed). Of the patients not seen for a second follow-up in PEG1, the majority (65%) had died or were too ill, including cognitive dysfunction. Changes in average MOS-Sleep scores over time were minor. Overall, EDS scores slightly increased from first to second follow-up, the within-person average difference was 3.0 (95% CI: -0.7, 6.6) points on the non-standardized score, i.e., on a scale from 0 to 100, whereas insomnia average scores did not change (-1.4, 95% CI: -4.6, 1.8). Figure 2 shows average within-person changes in insomnia and EDS scores, by PD severity measures, with t-tests comparing scores between groups at each follow-up time. At first follow-up, the severity measures UPDRS ≥ vs. <35 and LED ≥ vs.<500mg and a longer PD duration (≥ vs. <6.5y) were associated with worse concurrent insomnia scores, but these measures did not predict worsening of insomnia scores at the second follow-up. For EDS, on the other hand, higher PD severity and longer duration at first follow-up were associated with worse EDS scores at the second follow-up.

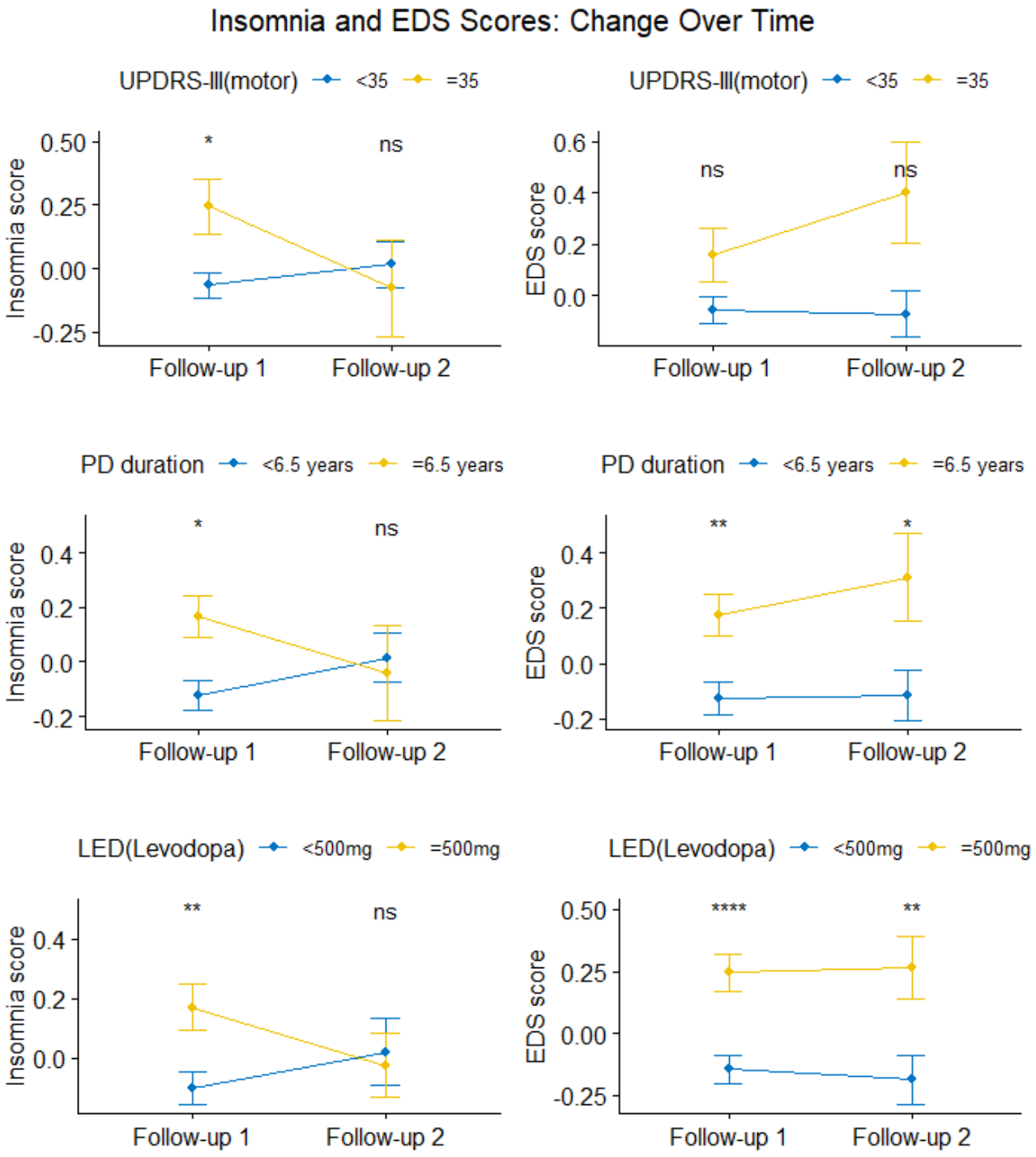


**Figure 2** Change in sleep scores from follow-up 1 to follow-up 2 (N=156), by PD severity measures at follow-up 1. Results of significance for t-test: *= p<0.05, **= p<0.01, ****=p<0.0001, ns= p>0.05.

## 4. Discussion

This large population-based study of Parkinson's disease assessed associations of PD clinical characteristics with insomnia and EDS symptoms among patients with on average six years of disease duration. For a subgroup of 156 patients, sleep information was collected again two years later. In this cohort, virtually all aspects of PD severity evaluated were associated either with worse insomnia, EDS, or with both sleep symptoms, confirming the burden of this non-motor problem during the progression of PD. Total motor UPDRS-III scores, sub-scores of tremor and limb bradykinesia, and UPDRS-IV motor fluctuations were associated with worse insomnia symptoms but not with EDS. Other aspects of PD, such as longer disease duration and motor sub-scores of axial/posture/gait and body bradykinesia were associated only with EDS symptoms. Levodopa doses ≥500mg and autonomic symptoms were associated with worse scores for both sleep problems. For the group with one additional follow-up, only EDS scores were slightly worse after 2.2 years on average, while insomnia scores remained similar.

Neurodegeneration of sleep-wake regulatory centers in PD resulting in circadian disruption [34] is one possible explanation for the association between worse total motor scores and insomnia. The finding that motor UPDRS total score and sub-scores of tremor, limb bradykinesia and motor fluctuations affect only insomnia symptoms can also indicate that these motor manifestations directly disrupt nighttime sleep. Since this study's patients are examined "off medication", those with high tremor sub-scores likely have worse tremor during off states at night. Worse tremor during night off states have been shown to lead to increased sleep fragmentation, resulting from re-emergence of resting tremor during micro-arousals, body movements and sleep-state changes (mainly from NREM to REM sleep) [35]. Similarly, limb bradykinesia during night off states may cause difficulties in turning and adjusting the body position in bed, which are problems known to cause sleep fragmentation in PD patients [11, 36]. It has also been shown previously [8] that motor activity from tremor or motor fluctuations may disrupt the circadian system directly, since body movements impact the physiological cues used by this system.

Three larger studies that related motor disability to insomnia have been descriptive and none have analyzed motor UPDRS sub-scores, but they corroborate the present study's findings for positive associations of overall motor severity and insomnia symptoms. A large population-based French study (COPARK), reported cross-sectional results for 636 PD patients who responded to the PSQI questionnaire [18] with a mean PD duration similar to our study (6.3 years) and found higher motor UPDRS total scores in those with sleep disturbance (defined as PSQI score above 5, similar in content to the MOS-sleep insomnia measure adopted here), but the results reported were unadjusted for potential confounders, such as age, gender and PD duration. A population-based Norwegian cohort (n=231) also reported insomnia to be associated with higher motor UPDRS total scores, but estimates from this study were not formally statistically significant and, again, unadjusted for potential confounders [17]. In addition, this population had a higher PD duration at time of study (average of 9.8 years for patients with insomnia and 7.8 for those without insomnia). The third study, a hospital-based longitudinal Dutch study (PROPARK) assessed sleep quality in 412 patients (average PD duration of 10.6 years) with 27% reporting insomnia; in cross-sectional analyses, these patients exhibited higher total motor UPDRS scores, and more motor complications and fluctuations [15].

Similar to the results presented here, an international multicenter study of 423 PD patients (mean PD duration of 6.7 years) reported no association between total motor UPDRS scores and concurrent EDS [20, 37], but they did not report results for motor UPDRS sub-scores. In the PEG population-based patient cohort presented here, the only motor UPDRS sub-score associated with EDS was axial/gait/posture, which includes body bradykinesia; however, PIGD motor subtype was not associated with higher EDS symptoms. Only one other study, using a specialty clinic population from China, has reported positive associations between body bradykinesia scores and EDS [21]. Compared with this study's population, the Chinese sample had slightly shorter average PD duration (5.1 years) and scored higher on the total motor UPDRS.

Given these results, and as suggested previously by others [38], EDS, unlike insomnia, does not seem to be directly related to PD motor dysfunction resulting from primary nigrostriatal dopaminergic degeneration, but rather to features that suggest the degeneration of other neurotransmitter systems characteristic of more advanced disease [11]. For example, in post-mortem and brain imaging studies in clinical samples [39], EDS has been related to the degeneration of the alertness system, including hypocretin neurons in the hypothalamus, noradrenergic neurons in the Locus Coeruleus, and serotonergic neurons in the Dorsal Raphe Nuclei. In this study's analyses, accounting for GDS scores in models for body bradykinesia and EDS moved the estimates towards no association, supporting the hypothesis [40] that depression in PD is associated with slowness of movement (body bradykinesia) and EDS; a future study will further explore the association of depression and sleep problems in the PEG cohort.

Therapy with levodopa and dopamine agonists is another factor frequently associated with sleep problems in PD in clinical practice. In general, the PEG study population seems to be under-treated, as almost one in 10 patients were not under any PD medication or treatment such as DBS [41], which could be credited to the study's source population being communities of mostly rural counties with intense agricultural activity, and low average education and income, where access to health care resources is often limited. Pharmacologically, it has been proposed that levodopa can affect circadian rhythms directly in PD patients through mechanisms that uncouple circadian rhythm and sleep regulation [34], such as altering melatonin secretion and action. In this study, levodopa doses (LED≥500mg/day) were associated with both insomnia and EDS symptoms, in similar magnitude, while dopamine agonists doses (LED≥200mg/day) did not affect sleep symptoms. Previous studies reported conflicting results regarding the contribution of levodopa therapy to sleep problems. A population-based study from Norway and a hospital-based Dutch study [19, 23, 24] found slightly higher LED in PD patients with EDS cross-sectionally, but LED did not predict worsening of EDS over time. The Norwegian ParkWest population-based cohort [19] reported no association of total LED and EDS for patients within five years from PD diagnosis, but a higher proportion of patients used dopamine agonists, 57% compared with 38% in our PEG cohort. Dopamine agonists have been shown to improve sleep in previous trials of rotigotine [42, 43], and to be associated with EDS and sleep-attacks in some clinical-based epidemiological studies [44], but not others [45]. No population-based studies addressed specific associations of dopamine agonists and sleep symptoms, and the present study may not have been able to detect associations if they are present, since only 38% of the study sample took such drugs.

Axial/gait/posture motor features of PD can be less responsive to dopaminergic therapy than tremor signs, which influence type and doses of PD medication prescribed [18]. Thus, to verify if these motor features can explain the association between levodopa and EDS, the models were

further adjusted for axial/gait/posture motor sub-scores. Interestingly, this did not change the coefficients for levodopa (LED≥500mg), but the coefficient for the motor sub-score was no longer statistically significant. This may indicate that the association of axial/gait/posture sub-scores and EDS is mediated through levodopa doses.

As shown here and previously reported [15, 19, 20, 46], non-motor and autonomic symptoms affect sleep quality and are related to EDS. Some of these manifestations can directly induce sleep fragmentation, such as nocturia. Others have been associated with circadian rhythms disruption, such as autonomic dysfunction. In fact, this study shows a strong association of sleep problems with autonomic symptoms including light headedness, constipation, drooling, chewing/swallowing, and urinary symptoms. This may not be surprising, as outputs from the suprachiasmatic nucleus, a structure in the hypothalamus recognized as the central pacemaker responsible for the regulation of circadian rhythms, innervates autonomous nervous system structures. Through these outputs, many independent circadian oscillators operate in peripheral organs and, coupled with hormonal secretion (involving melatonin and cortisol), they synchronize physiological functions, resulting, for example, in circadian fluctuations in blood pressure, urinary excretion and gastrointestinal activity. Degeneration of circadian system structures that induce circadian disruption would, thus, be manifesting in peripheral organs as autonomic dysfunction.

In the sub-group of 156 patients assessed twice for sleep problems during follow-up, insomnia scores did not worsen substantially, even when assessing subgroups with different PD severity (by UPDRS, PD duration, LED, and non-motor symptoms). On the other hand, EDS scores seem to worsen over time, especially in patients with worse PD severity at first follow-up, i.e., they reached the highest sleep score averages at their second follow-up. This may suggest that insomnia manifests early in the disease course, possibly concomitantly with worsening in tremor symptoms, but this sleep feature does not worsen as PD progresses. Two previous smaller studies examined progression of sleep symptoms in PD and also found insomnia prevalence to slightly decrease over follow-up time (8 years), while EDS worsened with PD progression [17, 19]. Future larger population-based longitudinal cohort studies of PD are still necessary to address how circadian dysfunction progresses in PD clinical course.

Lack of temporality is a limitation of this study. The main results reported are cross-sectional, while the exposures and outcomes studied are part of a vicious cycle of deterioration during PD progression and influence each other longitudinally. The associations reported here refer to prevalent sleep symptoms at on average six years after PD diagnosis, and we do not know when these sleep problems started. Another potential limitation refers to the absence of objective measures of sleep quality and structure, since we relied solely on self-reported information. This is, however, a problem common to all population-based studies with large numbers of patients, due to feasibility constraints that do not support using objective sleep laboratory assessments, such as polysomnography. Unmeasured residual confounding is unavoidable in observational research, however, the regression models took into account explicit hypothesized causal structures [33], different from purely predictive modeling approaches of insomnia and EDS in PD. Important strengths of this study are the large number of subjects and the population-based approach to identify PD cases, which likely yields estimates that are more representative of all PD patients, than those based on very selected clinic-based patient samples.

## 5. Conclusions

In conclusion, this study provides epidemiological evidence that motor and non-motor dysfunction in PD is associated with insomnia and EDS symptoms, but specific features and level of severity affect these sleep symptoms differently. While motor severity measured by total UPDRS score and sub-scores of tremor, limb bradykinesia and motor complications mainly impact insomnia, EDS symptoms were related to axial/gait/posture motor features, which may indicate higher levodopa doses and/or more advanced disease. Future assessments of sleep problems in longitudinal population-based studies are needed to help improve patients' overall health-related quality of life.

## Acknowledgments

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## Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Figure S1: Proposed Directed Acyclic Graph (DAG) depicting hypothesized relation of factors considered in cross-sectional analyses. Arrows in purple represent the main potential causal relations we aimed at estimating. Variables in parenthesis are not measured. UPDRS-III= measure of motor dysfunction severity. EDS= excessive daytime sleepiness.
2. Figure S2: Correlations among PD-related and sleep variables considered in analyses.

## Author Contributions

Jeff M Bronstein and Adrienne Keener conducted most of the clinical assessments of Parkinson's disease patients, at baseline and follow-up. Aline Duarte Folle conducted the analyses, with support from Kimberly Paul and Cynthia Kusters, and wrote the first draft of the paper, under supervision of Beate Ritz, who is responsible for the conception of the study. All authors contributed in discussing results and editing the manuscript.

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## Competing Interests

The authors have declared that no competing interests exist.

## References


1. Parkinson J. An essay on the shaking palsy. J Neuropsychiatry Clin Neurosci. 2002; 14: 223-236.
2. Mouret J. Differences in sleep in patients with Parkinson's disease. Electroencephalogr Clin Neurophysiol. 1975; 38: 653-657.
3. Tandberg E, Larsen JP, Karlsen K. A community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord. 1998; 13: 895-899.
4. Chaudhuri KR, Pal S, Dimarco A, Whately-Smith C, Bridgman K, Mathew R, et al. The Parkinson's disease sleep scale: A new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2002; 73: 629-635.
5. Videnovic A, Högl B. Disorders of sleep and circadian rhythms in Parkinson's disease. 1st ed. Vienna: Springer Vienna; 2015.
6. Suzuki K, Miyamoto M, Miyamoto T, Hirata K. Restless legs syndrome and leg motor restlessness in Parkinson's disease. Parkinsons Dis. 2015; 2015: 490938.
7. Li S, Wang Y, Wang F, Hu LF, Liu CF. A new perspective for Parkinson's disease: Circadian rhythm. Neurosci Bull. 2016; 33: 62-72.
8. Fifel K. Alterations of the circadian system in Parkinson's disease patients. Mov Disord. 2017; 32: 682-692.
9. Avidan A, Hays RD, Diaz N, Bordelon Y, Thompson AW, Vassar SD, et al. Associations of sleep disturbance symptoms with health-related quality of life in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2013; 25: 319-326.
10. Xu W, Tan CC, Zou JJ, Cao XP, Tan L. Sleep problems and risk of all-cause cognitive decline or dementia: An updated systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2019; 91: 1-9.
11. Stefani A, Högl B. Sleep in Parkinson's disease. Neuropsychopharmacology. 2020; 45: 121-128.
12. Daroff RB. The international classification of sleep disorders: Diagnostic and coding manual. Chest. 1991; 41: 160-160.
13. Marinus J, Visser M, Van Hilten JJ, Lammers GJ, Stiggelbout AM. Assessment of sleep and sleepiness in Parkinson disease. Sleep. 2003; 26: 1049-1054.
14. Sateia MJ. International classification of sleep disorders-third edition highlights and modifications. Chest. 2014; 146: 1387-1394.
15. Zhu K, van Hilten JJ, Marinus J. The course of insomnia in Parkinson's disease. Parkinsonism Relat Disord. 2016; 33: 51-57.
16. Porter B, MacFarlane R, Walker R. The frequency and nature of sleep disorders in a community-based population of patients with Parkinson's disease. Eur J Neurol. 2008; 15: 46-50.
17. Gjerstad MD, Wentzel-Larsen T, Aarsland D, Larsen JP. Insomnia in Parkinson's disease: Frequency and progression over time. J Neurol Neurosurg Psychiatry. 2007; 78: 476-479.
18. Ratti PL, Negre-Pages L, Perez-Lloret S, Manni R, Damier P, Tison F, et al. Subjective sleep dysfunction and insomnia symptoms in Parkinson's disease: Insights from a cross-sectional evaluation of the French CoPark cohort. Park Relat Disord. 2015; 21: 1323-1329.
19. Tholfsen LK, Larsen JP, Schulz J, Tysnes OB, Gjerstad MD. Development of excessive daytime sleepiness in early Parkinson disease. Neurology. 2015; 85: 162-168.

20. Amara AW, Chahine LM, Caspell-Garcia C, Long JD, Coffey C, Högl B, et al. Longitudinal assessment of excessive daytime sleepiness in early Parkinson's disease. J Neurol Neurosurg Psychiatry. 2017; 88: 653-662.
21. Xiang Y, Xu Q, Sun Q, Wang ZQ, Tian Y, Fang LJ, et al. Clinical features and correlates of excessive daytime sleepiness in Parkinson's disease. Front Neurol. 2019; 10: 1-9.
22. Junho BT, Kummer A, Cardoso F, Teixeira AL, Rocha NP. Clinical predictors of excessive daytime sleepiness in patients with Parkinson's disease. J Clin Neurol. 2018; 14: 530-536.
23. Tandberg E, Larsen JP, Karlsen K. Excessive daytime sleepiness and sleep benefit in Parkinson's disease: A community-based study. Mov Disord. 1999; 14: 922-927.
24. Zhu K, van Hilten JJ, Marinus J. Course and risk factors for excessive daytime sleepiness in Parkinson's disease. Parkinsonism Relat Disord. 2016; 20: 980-985.
25. Duarte Folle A, Paul KC, Bronstein JM, Keener AM, Ritz B. Clinical progression in Parkinson's disease with features of REM sleep behavior disorder: A population-based longitudinal study. Parkinsonism Relat Disord. 2019; 62: 105-111.
26. Wang A, Costello S, Cockburn M, Zhang X, Bronstein J, Ritz B. Parkinson's disease risk from ambient exposure to pesticides. Eur J Epidemiol. 2011; 26: 547-555.
27. Ritz B, Rhodes SL, Bordelon Y, Bronstein J. α-Synuclein genetic variants predict faster motor symptom progression in idiopathic Parkinson disease. PLoS One. 2012; 7: e36199.
28. Keener AM, Paul KC, Folle A, Bronstein JM, Ritz B. Cognitive impairment and mortality in a population-based Parkinson's disease cohort. J Parkinsons Dis. 2018; 8: 353-362.
29. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010; 25: 2649-2653.
30. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: Comparison with the unified Parkinson's disease rating scale. Mov Disord. 2013; 28: 668-670.
31. Höglund A, Hagell P, Broman J-E, Pålhagen S, Sorjonen K, Fredrikson S. A 10-year follow-up of excessive daytime sleepiness in Parkinson' s disease. Park Dis. 2019; 2019: 5708515.
32. Chaudhuri KR, Pal S, DiMarco A. The Parkinson's disease sleep scale: A new instrument for assessment of sleep, nocturnal disability and daytime sleepiness in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2002; 73: 629-635.
33. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999; 10: 37-48.
34. Mantovani S, Smith SS, Gordon R, O'Sullivan JD. An overview of sleep and circadian dysfunction in Parkinson's disease. J Sleep Res. 2018; 27: e12673.
35. French IT, Muthusamy KA. A review of sleep and its disorders in patients with Parkinson's disease in relation to various brain structures. Front Aging Neurosci. 2016; 8: 1-17.
36. Bhidayasiri R, Sringean J, Trenkwalder C. Mastering nocturnal jigsaws in Parkinson' s disease: A dusk‐to‐dawn review of night‐time symptoms. J Neural Transm. 2020; 127: 763-777.
37. Simuni T, Caspell-Garcia C, Coffey C, Chahine LM, Lasch S, Oertel WH, et al. Correlates of excessive daytime sleepiness in de novo Parkinson's disease: A case control study. Mov Disord. 2015; 30: 1371-1381.
38. Höglund A, Broman J-E, Pålhagen S, Fredrikson S, Hagell P. Is excessive daytime sleepiness a separate manifestation in Parkinson's disease? Acta Neurol Scand. 2015; 132: 97-104.

39. Wilson H, Giordano B, Turkheimer FE, Chaudhuri KR, Politis M. Serotonergic dysregulation is linked to sleep problems in Parkinson's disease. NeuroImage Clin. 2018; 18: 630-637.
40. Rampello L, Chiechio S, Raffaele R, Vecchio I, Nicoletti F. The SSRI, citalopram, improves bradykinesia in patients with Parkinson's disease treated with L-dopa. Clin Neuropharmacol. 2002; 25: 21-24.
41. Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA, Ritz B. Clinical characteristics in early Parkinson's disease in a central California population-based study. Mov Disord. 2005; 20: 1133-1142.
42. Vallderiola F, Compta Y, Aparicio J, Tarradellas J, Salazar G, Oliver JM, et al. Effects of night-time use of rotigotine on nocturnal symptoms in Parkinson's disease. Parkinsons Dis. 2015; 2015: 475630.
43. Pierantozzi M, Placidi F, Liguori C, Albanese M, Imbriani P, Marciani MG, et al. Rotigotine may improve sleep architecture in Parkinson's disease: A double-blind, randomized, placebo-controlled polysomnographic study. Sleep Med. 2016; 21: 140-144.
44. Homann CN, Wenzel K, Suppan K, Ivanic G, Kriechbaum N, Crevenna R, et al. Sleep attacks in patients taking dopamine agonists: Review. BMJ. 2002; 324: 1483-1487.
45. Ataide M, Franco CMR, Lins OG. Daytime sleepiness in Parkinson's disease: Perception, influence of drugs, and mood disorder. Sleep Disord. 2014; 2014: 1-5.
46. Matsubara T, Suzuki K, Fujita H, Watanabe Y, Sakuramoto H, Matsubara M, et al. Autonomic symptoms correlate with non-autonomic non-motor symptoms and sleep problems in patients with Parkinson's disease. Eur Neurol. 2018; 80: 193-199.

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Editorial

# Driving Skills in Older Adults

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The percentage of the older population is rapidly increasing worldwide. It has been estimated that by the year 2050, one-third of the population in the OECD countries will be above 65 years. This demographic change will increase the number of older people who want to or have to stay mobile because of economic conditions. Mobility is a key to healthy aging as it is related to the basic human need for physical movement. Mobility is associated with a person's physical and psychological well being. Driving one's car is a popular mode of transport in developed countries. Cessation of driving can lead to a range of detrimental consequences, such as a decrease in social activities, which impacts cognitive health. Besides, restriction to car driving can force older people to use less safe modes of transport, making them more vulnerable to accidents. Hence, older adults should continue driving their cars as much as possible.

Driving is an activity that takes place in a dynamic environment requiring sensory, motor, and cognitive functions. With increasing age, a decline in most of these functions has been observed. However, changes in functions differ among individuals and are influenced by a multitude of environmental and lifestyle factors. Such functional changes may affect the performance of

everyday tasks, especially complex activities. Indeed, visual and cognitive factors can explain most of the age-related changes in the ability to drive safely.

Since most of the traffic-relevant information is perceived by the visual system, age-related changes in vision are the most relevant for driving. Such changes include reductions in visual acuity and contrast sensitivity, increased glare sensitivity, and reduced field of view. Motor changes include diminishing muscle strength and movement speed, which may slow down emergency actions or prolong braking time. Furthermore, neck flexibility is essential during driving and is strongly reduced with age. Finally, motor coordination and dexterity also deteriorate with increasing age.

Cognitive issues in older adults are often overlooked despite their high importance in driving. In particular, the so-called executive functions, which control lower-level functions, are highly relevant for driving. Executive functions include inhibition of irrelevant information, updating of memory, and switching between tasks. Besides, they control attention, which is necessary for visual search and attention switching and distribution. For example, visual search, that is, the scanning of the visual scene to detect a target stimulus is mostly impaired in people in their 60s. Hence, in real traffic, important targets and threats are possibly detected later or none by older adults.

Cognitive problems increase in mild cognitive impairment (MCI), which is present in many older adults. Drivers with MCI have enhanced driving problems than those without MCI.

Safe driving depends not only on skills but also on personality factors like self-rating, confidence, risk acceptance, or sensation-seeking. Most of the older adults are overconfident regarding their driving skills and rate themselves as good or excellent drivers regardless of their actual performance. This may impair their motivation to take measures to improve their driving.

Despite impaired functions and overestimated driving performance, older adults often drive inconspicuously. This is because routine traffic situations such as highway driving rely mainly on highly automated processes, which show a less age-related decline. Moreover, to cope with more complex situations, many older adults develop compensation strategies such as slow driving and selection of well-known routes. Also, compensation mechanisms such as a stronger preparation in complex situations are frequently observed among the older population. However, some of those strategies are not satisfactory since they may encumber other drivers (e.g., slow driving) or the driver himself (e.g., avoidance of certain routes).

Nevertheless, the accident rate among older adults, based on distance driven estimates, is relatively high. In particular, drivers aged above 75 years who drive less than 3000 km per year have the highest accident risk. Moreover, 75% of drivers aged 75 and above who are involved in an accident are primarily responsible for the accident. A closer look at the accidents shows that they occur in specific situations such as turning, driving backward, and complex traffic junctions. However, accident rates underestimate the problems since, in most critical situations, accidents can be avoided by the driver himself or by other traffic participants. More often, near-accidents likely happen that do not show up in the statistics but may be remarked by fellow passengers.

Apart from having problems in certain situations, older adults are also more vulnerable than younger adults due to their fragile body structure. For example, the bones and ribs are not flexible in old age, which can be aggravated by osteoporosis, a common disease in older adults. Such lower flexibility usually leads to more serious injuries, and even safety belts could cause fatal injuries in old adults.

Even more vulnerable are older adults who drive bicycles. Riding a bicycle not only requires the skills of car driving, that is, coping with complex situations and interacting with other drivers, but also the skills of handling the bicycle, which is not performed automatically as handling a car. Many older adults who have not used their bicycles for years have poor cycling skills, which are often not realized by the cyclist. Hence, accident rates among older cyclists increase steadily and mainly while using e-bikes with their weight and speed.

Another issue among older adults is fatigue. Many accidents happen when the driver is fatigued. Most of the older adults suffer sleeping problems and hence are more fatigued than younger adults. On the other hand, there is some evidence that older adults are more resistant to fatigue. The question is about the marginal conditions under which older drivers are more or less vulnerable to fatigue than younger drivers.

These facts show that measures are necessary to increase safety and support for older drivers. In several countries, to increase safety, medical and psychological tests are mandatory for older adults to renew their driving license. However, this does not necessarily mean that safety is increased. For example, the number of fatal accidents in Finland, which requires a medical test for older drivers, is not lower than in Sweden, a country with no such test. One reason for such failures is the type of tests required. Usually, only cursory and short medical tests are used. When cognitive tests are given, they are often designed for dementia diagnosis, such as the Mini-Mental State Examination (MMSE). Such tests are unsuitable for measuring the physical, sensory, and cognitive skills that are essential for driving.

The most important issue is the identification of unfit older drivers. An obvious and direct method is an on-road driving assessment, usually conducted by a driving instructor, who is sometimes accompanied by a traffic psychologist. Meanwhile, there are standardized and even PC-based driving protocols that aim at more objectivity. However, such on-road assessments are costly and require appropriate equipment and time resources. Besides, the real traffic is not always challenging, which depends on the time and location of the assessment ride, and of course, on the competence and experience of the driving instructor. Hence, the elderly may show no problems even though they would probably be revealed in complex situations. An alternative is to drive using a driving simulator, which has the advantage of administering and repeating sufficiently difficult scenarios. As with driving tests in real traffic, this methodology requires adequate equipment and skilled experts to yield reliable results. Also, the feeling of being in real traffic is absent in simulators, while there is often simulator sickness with older adults. A third and promising alternative is to administer off-road tests for cognitive function as well as visual and motor functions that are important for driving. This reminds of the periodic car inspection in which functions of the car and not its behavior in real traffic is checked. The crucial issue with such testing is the selection of the most appropriate tests for sufficiently predicting driving fitness and accident rate. Single and ill-chosen tests have no predictive power. However, carefully compiled test batteries that include tests of the most important functions relevant for driving appear to have high predictive power. Such off-road assessments should also include interviews that ask for risk factors such as avoidance behavior, reports of unsafe driving by relatives, the number of (minor) accidents in the past years, and reduced driving practice.

All those assessment methods are only meaningful if they are accompanied and followed by measures to support older drivers, and in particular, those who have driving problems. Otherwise, assessments are likely avoided if voluntary, and dreaded if mandatory. Such measures could either

be information and guidance campaigns, the design of age-friendly traffic and car environments, or training measures that are aimed at improving the individual driving skill of an older driver.

Information campaigns address the older public, giving information about factors that influence driving fitness (e.g., certain diseases and drugs), about strategies on how to cope with certain driving situations, and about training possibilities to increase driving performance. They are relatively easy to organize. However, the success of such campaigns depends on whether they are accompanied by practical courses in groups.

Certain traffic situations, such as turning left at complex crossroads, are particularly difficult for older drivers and can be decreased by age-friendly street design. For example, left turns should be protected by traffic lights or by well-visible guidelines. Also, at crossroads or roundabouts, distracting and traffic-irrelevant information such as advertisements should be minimized. Complex areas should be structured and traffic routing distinctly marked by coloring. On the other hand, well-designed car technology such as high doors and seats and broad circumferential visibility can help elderly drivers. Above all, route guidance systems are highly important for the elderly since they reduce the need for memory and visual search. However, to be helpful and not distracting, such systems have to meet certain requirements.

The third measure is individual training for older drivers. The most straightforward training is to take driving lessons with a driving instructor in real traffic. They require well-trained driving instructors who know the problems of older drivers as well as sufficiently difficult traffic locations. If the training is properly conducted, such driving lessons can strongly improve driving fitness in older drivers, and also for poor drivers.

An off-road variant is the training of specific skills (such as visual search) or coping with difficult driving scenarios with the help of programs running on a personal computer or a driving simulator. The personal computer has the advantage of being affordable and widely available, so it might be possible to conduct such training at home, after proper instruction.

A further possibility is the direct training of functions that are necessary for driving, in particular motor, and cognitive functions. For example, head movements and strength can be trained and result in improvements in the trained functions.

In the cognitive domain, visuospatial skills and spatial attention can be trained; the latter results in better and longer driving skills. Besides, physical training is known to improve motor and cognitive functions. However, there are only a few studies which show improvements in driving fitness after undergoing such training. Since training can be conducted at home, further studies on this topic are warranted.

The present special issue aims at addressing most of the mentioned issues and any other issue concerning older drivers and how to help them keep driving as long as possible.

**Author Contributions**

Michael Falkenstein did all the research work for this study.

**Competing Interests**

The author has declared that no competing interests exist.


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Research Article

# Establishing a Method for Quantifying Spinal Curvature during Videofluoroscopic Swallow Studies: Applying the Modified Cobb Angle to Healthy Young and Older Adults

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**Abstract**

The Cobb angle is traditionally used for quantifying the degree of spinal curvature through evaluation of the full spinal cord. When conducting measurements on videofluoroscopy swallowing studies (VFSS), the Cobb angle can measure degree of cervical vertebrae curvature, which may have implications for swallowing. Given that this measure may have utility in dysphagia research, the reliability of this measure taken from C2-C4 and establishing the presence of changes with age were the focus of the current, proof-of-principle study. VFSS from 19 healthy young adults and 39 healthy older adults were

retrospectively analyzed. The C2-C4 Cobb angle was measured between cervical vertebrae two and four on frames of laryngeal vestibule closure (LVC) and post-swallow rest. Results revealed excellent levels of inter- and intra-rater reliability for frame of post-swallow rest (ICCs = 0.788 and 0.793), and fair to good levels of agreement for frame of LVC (ICCs = 0.667 and 0.621). Significant differences in the C2-C4 Cobb angle were found between the healthy young and old data ($p < 0.01$). Healthy younger adults had a mean angle of 5.8±9.0 degrees at LVC and 7.7±4.5 degrees at swallow rest, whereas healthy older adults had a mean angle of 12.5±9.0 degrees at LVC and 12.4±9.7 degrees at rest. Consistent with the existing spine literature, the curvature of cervical vertebrae appears to increase with age. With established reliability, we propose that the C2-C4 Cobb angle may be used to determine the degree of spinal curvature in a variety of patient populations in order to determine impacts on swallowing function.

**Keywords**
Deglutition; dysphagia; healthy adults; spine; assessment; videofluoroscopy

## 1. Introduction

Given the rapidly growing population of older adults, it is important to consider how natural and expected changes to the body – specifically to the head and neck – due to aging, might impact swallowing function. Research has previously established that with age we can expect changes to pharyngeal lumen size [1], tongue strength [2] and timing of the swallow [3], amongst other things. Something rarely considered when examining swallowing in older adults is their posture, which is influenced by the shape or curvature of the spine [4]. Interestingly, most previous research suggests that body position has little impact on swallowing [5, 6]. However, one study by Su and colleagues quantified swallowing parameters in both an upright and supine position and determined that positioning had little impact on swallowing a thicker consistency, like pudding, but saw increases in temporal measures when thin liquids were swallowed in the supine position [7]. Anecdotally, clinicians encourage patients to sit upright as close to 90 degrees as possible in order to promote optimal swallowing function. They suggest that any sitting position less than 90 degrees may prevent the efficient passage of the bolus from the oral cavity into the esophagus [8-10]. The focus is on the sitting position and resulting posture, with little consideration of how the natural shape of the spine might influence swallowing function.

Studies analyzing anteriorly protruding cervical osteophytes, which are bony protrusions on the anterior surface of the lower cervical vertebrae, suggest that such changes to the spine impinge bolus passage into the cervical esophagus leading to increased pharyngeal residue and reduced upper esophageal sphincter opening [11-13], and/or altered sensation [14-16], as well as laryngeal penetration [17, 18]. Other than this research, few studies outside of the traumatic spinal cord injury literature have examined the relationship between the changes to the spine and its impact on swallowing physiology and mechanics. Given that swallowing function post-spinal cord injury is dependent on the cause and type of injury [19], we cannot use such studies to make inferences about how non-injury related differences in spinal curvature might affect swallowing. Research

specific to the cervical spine has suggested that kyphosis may result in pharyngeal phase deficits [20] and increased risk of aspiration [21]. Moreover, spinal-specific research has previously established that as one ages the degree of kyphosis (i.e. outward curvature of the spine causing "hunching" of the back [see Figure 1]) is expected to increase along the full spine [22-24]. Other research has postulated that neck posture can influence one's risk of aspiration [25-30]. For example, a few studies have suggested that neck flexion in the form of a chin-down posture improves laryngeal vestibule closure and epiglottic angle, resulting in reduced incidences of airway invasion [25, 31, 32]. Since kyphosis is expected with age and neck flexion may act as a protective mechanism during swallowing, one might assume that age-related changes in the spine might positively influence swallowing physiology.

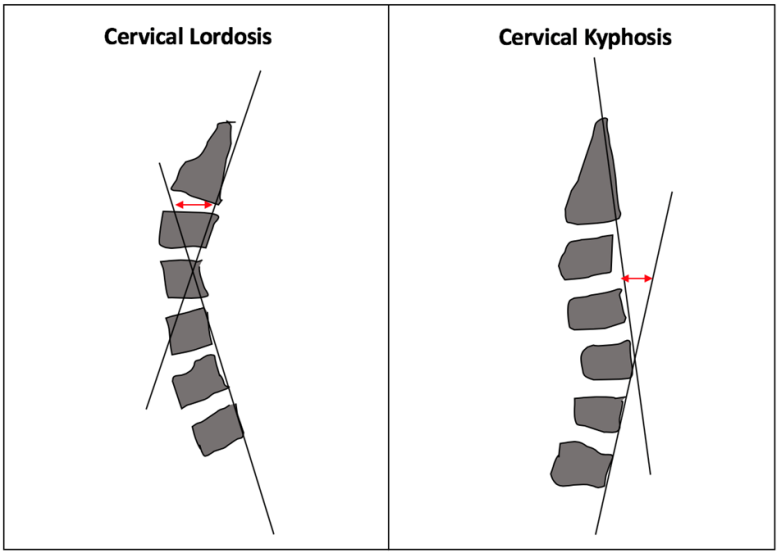


**Figure 1** A lordotic spine (left) versus kyphotic cervical spine (right).

The spinal cord literature has provided some evidence of age-related changes to the cervical spine. A recent meta-analysis examined the existence and extent of cervical lordosis in asymptomatic individuals, and evaluated the relationship of this lordosis with age and gender [33]. Upon analyzing 21 studies, the authors found curvature was not significantly different between symptomatic and asymptomatic individuals, and age was not significantly associated with amount of lordotic cervical curvature. Interestingly, other studies have found that the angle of cervical lordosis tends to increase with age [34-37]. The parameter of interest for all of these studies was cervical lordosis – where the spine is curving posteriorly (see the image to the left of Figure 1). However, it is unknown whether kyphosis (anterior curvature or forward head posture) is seen specifically in the cervical vertebrae. These studies also all employed the C2-C7 (cervical vertebra two to cervical vertebra seven) Cobb angle to measure cervical curvature [38].

The Cobb angle has historically been used to quantify the degree of spinal curvature for patients with scoliosis through evaluation of the full spinal cord and has been established as reliable in this context [39]. This method defines angles between 20° and 60° as normal cervical curvature [20]. Typically, to measure the Cobb angle, a right angle is drawn between the top-most and bottom-most curved vertebrae, and measure the angle formed between the intersecting rays from each right angle (Figure 2). The C2-C7 Cobb method measures the curvature of the full

cervical spine using radiographic images [39]. Videofluoroscopy swallowing studies (VFSS) are dynamic x-ray videos that are used to assess swallowing physiology and mechanics, with radiographic images taken depicting the region of the nasal cavity to the cervical esophagus. While a VFSS results in series of radiographic images, more often than not, all cervical vertebrae are not visible. More specifically, it is often difficult to clearly discern C5-C7. Given that C4 (cervical vertebra 4) is generally much more readily visible, we wanted to determine if the Cobb angle could be measured between C2 and C4, rather than between C2 and C7. In essence, the C2-C4 would act as a proxy measure, allowing a clinician to screen for cervical spine changes using VFSS data, rather than subjecting patients to a separate x-ray study of the spine. Interestingly, measures conducted between C2-C4 have become common in the dysphagia literature [40-44], likely due to the fact that they are clearly visible on VFSS, which is the gold standard method for evaluating swallowing. Since we do not currently have an established method for determining degree of cervical curvature on frames taken from VFSS, this was the primary purpose of the current, exploratory, proof-of-principle study. As a first step in this concept development, we aimed to establish if measurements taken from C2 to C4 were reliable. This would help to determine the potential of using the modified method as a proxy measure, instead of the traditional C2-C7 measurement. If the C2-C4 measurements were found to be reliable, we also aimed to determine if differences in cervical spine curvature measured were seen between healthy young and healthy old participants, consistent with previous spinal cord literature. Moreover, C2-C4 is highly correlated with participant height and thus frequently used in dysphagia research for scaling measures [40, 45]. We hypothesized that a) we could reliably measure the Cobb angle between C2 and C4 and b) that we would see a significant increase in the Cobb angle with age.

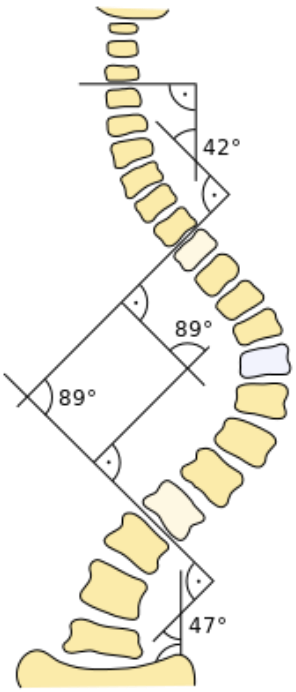


**Figure 2** This image depicts the typical method for measuring the Cobb angle. This image by Skoliose-Info-Forum.de is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.

## 2. Materials and Methods

### *2.1 Data Collection*

The inclusion criteria for the database were that participants were either young adults between 18 and 45 years of age and healthy, or older healthy adults above 65 years of age. The database consisted of videos used for the sole purpose of research. Exclusion criteria for all participant in the database included a history of dysphagia, neurological disease/insult, significant head and neck surgery (other than routine dental surgery, tonsillectomy, or adenoidectomy), major spinal deformities, chemoradiation to the head and neck, and/or possible pregnancy. Ultimately, VFSS were included from 19 healthy young adults (10 males; mean age: 32; range: 22-45) and 39 healthy older adults (18 males; mean age: 77; range: 65-95). VFSS were excluded if image quality and/or positioning of the participant prevented the spine from being viewed clearly (n=6, 1 younger adult and 5 older adults). All studies were conducted using a Kay Pentax Digital Swallow Workstation recording system, with the fluoroscope in lateral view at 30 pulses per second and were captured and recorded at 30 frames per second.

Data for this study were extracted from a retrospective research archive of VFSS. The original studies were approved by the research ethics boards at Toronto Rehabilitation Institute and New York University, and written consent was obtained from each participant prior to study participation.

### *2.2 Data Processing*

Data extraction for this study was restricted to clips of the first, single sip of thin liquid for each participant (continuous cup and straw drinking were excluded). Using standard desktop computers with i7 processors and labs with dim lighting so that the x-ray images were clearly visible, the VFSS were first spliced into bolus-level clips using Corel Video Studio Pro. They were then assigned an alphanumeric code. Raters were a speech-language pathologist and a speech-language pathology graduate student who had 4 years and 1 year, respectively, of previous experience performing frame-by-frame analyses of VFSS, including identifying swallowing physiology, events and kinematics [41]. For the purposes of this study, raters underwent further training on how to measure the Cobb angle. Given the potential for spine angle differences during swallowing and at rest, the raters were asked to identify two frames per participant. First, they identified the frame of maximum laryngeal vestibule closure (LVC), defined as the first frame where there was maximum approximation of the arytenoids to the laryngeal surface of the epiglottis. They also identified the frame of post-swallow rest, defined as the first frame showing the pyriform sinuses at the lowest position, relative to the spine, prior to any hyoid burst or laryngeal elevation for a subsequent subswallow. These two frames were chosen with the intent of capturing the spine angle during the height of the swallow (LVC; i.e. during swallowing) and capturing the spine angle at rest where it would be unlikely for the posture to be influenced by swallowing. Post-swallow rest, rather than pre-swallow bolus hold, was chosen as a frame of rest given that data were extracted retrospectively and not all participants performed bolus holds during their VFSS. Further, the ASPEKT (Analysis of Swallowing Physiology: Events, Kinematics and Timing) method [41] is regularly employed in the lab, and this method requires several measures to be taken at the frame

of LVC and at the frame of post-swallow rest. Given the high reliability of identifying these frames, we felt it best to choose these frames for the current study.

### *2.3 Videofluoroscopy Rating*

Once frames of LVC and post-swallow rest were identified and agreed upon, the degree of cervical spine curvature was measured using the Cobb angle. For the current study, the Cobb angle was measured between C2 and C4 in lateral-view VFSS using the angle tool in ImageJ (https://imagej.nih.gov/nih-image/) on the pre-established frames of LVC and post-swallow rest for thin liquid swallows (Figure 3). These vertebrae were chosen because they tend to be consistently and most easily visible on a VFSS. Further, C7 was not visible in any of the VFSS in our database, likely due to the fact that the shoulder generally obstructs the view of the inferior cervical spine when patients are positioned in the lateral view. C2-C4 appeared far enough apart to obtain a measure of curvature. Raters used the ROI Manager within ImageJ to allow each angle drawn to remain on the screen while subsequent angles were drawn, and measurements were taken. Twenty percent of the measures were taken in duplicate in order to calculate inter- and intra-rater reliability.

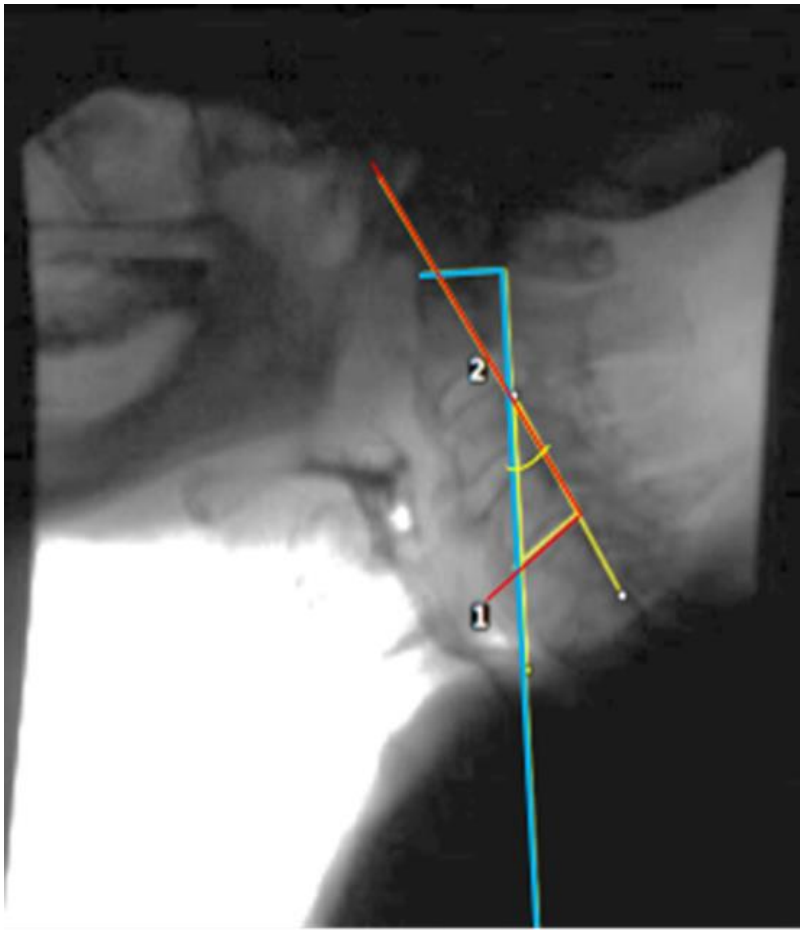


**Figure 3** Example of two 90°angles around superior portion of C2 (angle 2, in blue) and the inferior portion of C4 (angle 1, in red) intersect to measure the Cobb angle (in yellow).

### *2.4 Data Analysis*

All statistical analyses were conducted in IBM SPSS version 25. First, all reliability measures were computed using two-way mixed intraclass correlation coefficients (ICCs) for consistency. A priori determined cut-offs for acceptable reliability were established. Intra- and inter-rater reliability assess agreement of the same rater with themselves (intra) or with a second rater (inter). Intra- and inter-rater reliability ICCs of 0.75 and above are considered to have 'excellent' reliability [46]. Next, descriptive statistics were calculated to describe mean cervical curvature for each participant group at both frame of LVC and frame of post-swallow rest. Independent sample t-tests were used to compare degree of curvature at each time point between healthy young and healthy old. Two-tailed p-values $p < .05$ were considered statistically significant. Effect sizes for significant pairwise comparisons were calculated using Cohen's d. Cohen's d can be interpreted as showing a small effect size for values of < 0.5, medium effect size for values of 0.5–0.8, and large effect size for values of > 0.8 [47].

## 3. Results

Results revealed excellent levels of agreement within and across raters for degree of C2-C4 curvature on the frame of post-swallow rest (ICC = 0.793 (95%CI [-0.032, 0.959]) and 0.788 (95%CI [0.060, 0.952]), respectively). There were fair to good levels of agreement within and across raters for frame of LVC (ICC = 0.621 (95%CI [-0.893, 0.924]) and 0.667 (95%CI [-0.476, 0.925]), respectively).

Descriptive statistics for the parameters of interest (modified Cobb's angle measured at LVC and post-swallow rest) are displayed in Table 1. Significant differences in the C2-C4 Cobb angle were found between healthy young and healthy old at post-swallow rest ($t(55) = 2.035$, $p = 0.003$; Cohen's $d = 0.633$ [medium]). Significant differences in the C2-C4 Cobb angle were also found between the healthy young and healthy old data at frame of LVC ($t(56) = 3.140$, $p = 0.001$; Cohen's $d = 0.97$ [large]). No significant differences were found between C2-C4 Cobb angle measured from frame of LVC compared to frame of post-swallow rest across collapsed age groups ($t(81) = -0.809$, $p = 0.421$).

**Table 1** Descriptive statistics for the modified Cobb angle measured across samples at two different timepoints: laryngeal vestibule closure (LVC) and post-swallow rest.

| Measure | Healthy young (n = 19) | Healthy old (n= 39) | P-value |
|---|---|---|---|
| **C2-C4 angle at frame of LVC (mean ± standard deviation)** | 5.8 ± 9.0° | 12.5 ± 9.0° | 0.001* |
| **C2-C4 angle at frame of post-swallow rest (mean ± standard deviation)** | 7.7 ± 4.5° | 12.4 ± 9.7° | 0.003* |

*Denotes a statistically significant p-value, per the results of t-test.

## 4. Discussion

The primary objectives of this proof-of-principle study were to establish a reliable method for measuring cervical spine curvature on VFSS and determine if differences existed in cervical spine curvature between healthy young and healthy old samples. Our findings revealed that the C2-C4 Cobb angle may be a reliable method to measure cervical spine curvature, particularly when measured on frame of post-swallow rest. In addition, we found significant differences in curvature between younger and older healthy participants. More specifically, consistent with the existing spinal cord literature, cervical vertebrae two to four appear to increase in curvature with age [22-24, 35-38].

It is interesting to note that reliability is more clearly established on frame of post-swallow rest compared to frame of LVC. The reduced reliability on frame of LVC could be due to the movement inherent within the pharyngeal stage of the swallow, causing artifact within that frame so that the borders of the cervical vertebrae were not completely clear to raters. The overall quality of the videos may have also played a role in making the necessary ratings. Given that no significant differences were found between the C2-C4 Cobb angle at frame of LVC compared to frame of swallow rest, we recommend that future use of the C2-C4 Cobb angle in this context be performed on frame of post-swallow rest over the frame of LVC. It may be warranted to explore other frames of interest in future research.

This non-invasive method of measuring cervical spinal cord curvature has potential use for future dysphagia research. With established reliability, the C2-C4 Cobb angle can be used to determine the degree of spinal curvature in a variety of populations and potentially explore its impact on swallow biomechanics. In order to further establish reliability, it is important that this method is validated by comparing the results to the standard application of the Cobb angle from C2-C7 and by evaluating the efficacy of this measurement in patients with documented cervical spine changes. Once confirmed to be reliable and valid, the modified method might specifically be useful in situations where we expect damage to or deterioration of the cervical spine, without having to request a separate x-ray to take measurements on the full cervical spine using the C2-C7 Cobb method. Moreover, the measurements can be incorporated into statistical analyses to control for variation attributed to spinal curvature during swallowing. They might also be used as a method of monitoring changes in spinal curvature within older adults along the course of a disease trajectory. Some might also choose to use measurements of C2-C4 spine curvature to help explain changes in the swallow that cannot be attributed to timing, coordination or basic kinematics. This proxy measure might eventually be useful for clinicians who are concerned about neck posture and would like to track changes in cervical spine curvature via clinical VFSS performed over time.

When considering that significant differences in C2-C4 curvature were found between the young and older participants, one might question the reason for these changes across the lifespan. Recent research by Brates et al. [40] suggests that changes to spinal morphology result in scaled hyoid movements that are inflated in older individuals because of a reduction in C2 to C4 length, due to cervical disc degeneration present in most older adults [48]. This degeneration results in a loss of intervertebral height. It is possible that this difference in C2 to C4 length may be impacting the Cobb angle, or an increase in kyphosis is contributing to a shorter cervical spine height. Future work will need to consider these age-related changes to the spine and clarify how kyphosis and

disc degeneration are related. In order to monitor these changes over time, we will also need to establish test-retest reliability.

Given that the purpose of the current, exploratory study was to establish proof-of-principle, several limitations require acknowledgement. Firstly, the method itself has some limitations. Since it is measuring spine curvature between a relatively short distance (3 vertebrae), the resulting measurements may not account for disc protrusion, osteophytes, or other factors influencing spine curvature that occur below C4. However, given that the region between C2 and C4 is where many important physiologic swallowing functions take place, we predict that curvature in this area is significant for swallowing physiology and is therefore useful to measure. Another limitation is that the data analyzed for this study was restricted to a retrospective sample of young and older healthy adults, who did not have any documented cervical spine changes. A further limitation is that given that the data were extracted retrospectively from a research archive, it is possible that differences in head posture, patient positioning and/or instructions across participants may have impacted the findings. We were also unable to compare our C2-C4 Cobb angle measurements to measurements taken from C2-C7, given that C7 was not visible on the large majority of VFSS. Future studies should consider validation against x-ray where more of the spine is visible and/or MRI. Moving forward, it will be critical to perform a prospective study, where many of these factors can be controlled. Future studies should also consider minimizing random error by taking a minimum of three measurements and averaging the results.

## 5. Conclusions

The Cobb angle is a method of measuring spine curvature on x-rays and is a relatively simple measurement to conduct. This proof-of-principle research establishes that the Cobb angle measurements between cervical vertebrae two and four, derived from VFSS using ImageJ on the frame of post-swallow rest, have satisfactory inter-rater and intra-rater reliability. Moreover, we have confirmed changes in cervical spine curvature with age using this modified Cobb angle method, thus suggesting that the measure may be an option for monitoring cervical spine curvature via VFSS. Future work should focus on recruiting a prospective sample that includes patients with documented cervical spine changes that are age-matched with healthy participants. It would also be interesting to determine if the trend of increased C2-C4 spine curvature continues with old, old adults (i.e. those who are 80+ years of age). Given that cervical spine curvature may be influenced by posture and thoracic spine curvature, future work should compare these parameters to measurements taken using a cervical range of motion device, used to evaluate the range of motion of the cervical spine. Validation of this method within a prospective study using the C2-C7 Cobb method will also be an important next step towards using this adapted method in research and clinical practice. Lastly, future studies should determine if and at what point cervical kyphosis influences swallowing physiology. The directionality of the curvature must also be confirmed, as well as the implications of lordotic and kyphotic cervical spines on swallowing function in different populations and in various swallowing postures.

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**Author Contributions**

ANM: conception, experiment design, data analysis, drafted, and revised manuscript; LFR: conception, experiment design, and revised manuscript; SMM: conception, experiment design, data collection, data analysis, and revised manuscript.

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**Competing Interests**

The authors have declared that no competing interests exist.

**References**

1. Molfenter SM, Lenell C, Lazarus CL. Volumetric changes to the pharynx in healthy aging: consequence for pharyngeal swallow mechanics and function. Dysphagia. 2019 ;34: 129-137.
2. Fei T, Polacco RC, Hori SE, Molfenter SM, Peladeau-Pigeon M, Tsang C, et al. Age-related differences in tongue-palate pressures for strength and swallowing tasks. Dysphagia. 2013; 28: 575-581.
3. Namasivayam-MacDonald AM, Barbon CEA, Steele CM. A review of swallow timing in the elderly. Physiol Behav. 2018; 184: 12-26.
4. Raine S, Twomey LT. Head and shoulder posture variations in 160 asymptomatic women and men. Arch Phys Med Rehabil. 1997; 78: 1215-1223.
5. Barkmeier JM, Bielamowicz S, Takeda N, Ludlow CL. Laryngeal activity during upright vs. supine swallowing. J Appl Physiol (1985). 2002; 93: 740-745.
6. Dejaeger E, Pelemans W, Ponette E, Vantrappen G. Effect of body position on deglutition. Dig Dis Sci. 1994; 39: 762-765.
7. Su HK, Khorsandi A, Silberzweig J, Kobren AJ, Urken ML, Amin MR, et al. Temporal and physiologic measurements of deglutition in the upright and supine position with videofluoroscopy (VFS) in healthy subjects. Dysphagia. 2015; 30: 438-444.
8. Palmer JB, Kuhlemeier KV, Tippett DC, Lynch C. A protocol for the videofluorographic swallowing study. Dysphagia. 1993; 8: 209-214.
9. Alghadir AH, Zafar H, Al-Eisa ES, Iqbal ZA. Effect of posture on swallowing. Afr Health Sci. 2017; 17: 133-137.
10. Sutthiprapaporn P, Tanimoto K, Ohtsuka M, Nagasaki T, Iida Y, Katsumata A. Positional changes of oropharyngeal structures due to gravity in the upright and supine positions. Dentomaxillofac Radiol. 2008; 37: 130-135.
11. Granville LJ, Musson N, Altman R, Silverman M. Anterior cervical osteophytes as a cause of pharyngeal stage dysphagia. J Am Geriatr Soc. 1998; 46: 1003-1007.
12. Stuart D. Dysphagia due to cervical osteophytes. Int Orthop. 1989; 13(2): 95-99.
13. Yin T, Jardine M, Miles A, Allen J. What is a normal pharynx? A videofluoroscopic study of anatomy in older adults. Eur Arch Otorhinolaryngol. 2018; 275: 2317-2323.

14. McCulloch TM, Jaffe D. Head and neck disorders affecting swallowing. GI Motility online. 2006.
15. Kim MJ, Chung TS, Lee JT, Yoo HS, Suh JH, Chang TY, et al. Radiologic evaluation of the globus symptom using videotape recorder. J Korean Radiol Soc. 1988; 24: 381-389.
16. Egerter AC, Kim ES, Lee DJ, Liu JJ, Cadena G, Panchal RR, et al. Dysphagia secondary to anterior osteophytes of the cervical spine. Global Spine J. 2015; 5: e78-e83.
17. Seidler TO, Alvarez JP, Wonneberger K, Hacki T. Dysphagia caused by ventral osteophytes of the cervical spine: clinical and radiographic findings. Eur Arch Otorhinolaryngol. 2009; 266: 285-291.
18. Frempong-Boadu A, Houten JK, Osborn B, Opulencia J, Kells L, Guida DD, et al. Swallowing and speech dysfunction in patients undergoing anterior cervical discectomy and fusion: A prospective, objective preoperative and postoperative assessment. J Spinal Disord Tech. 2002; 15: 362-368.
19. Valenzano TJ, Waito AA, Steele CM. Characterizing dysphagia and swallowing intervention in the traumatic spinal injury population. Dysphagia. 2016; 31: 598-609.
20. Papadopoulou S, Exarchakos G, Beris A, Ploumis A. Dysphagia associated with cervical spine and postural disorders. Dysphagia. 2013; 28: 469-480.
21. Kim SK, Mo SJ, Moon WS, Jun PS, Kim CR. Effects of cervical kyphosis on recovery from dysphagia after stroke. Ann Rehabil Med. 2016; 40: 816-825.
22. Hinman MR. Comparison of thoracic kyphosis and postural stiffness in younger and older women. Spine J. 2004; 4: 413-417.
23. Katzman WB, Wanek L, Shepherd JA, Sellmeyer DE. Age-related hyperkyphosis: Its causes, consequences, and management. J Orthop Sports Phys Ther. 2010; 40: 352-360.
24. Fon G, Pitt M, Thies A. Thoracic kyphosis: Range in normal subjects. Am J Roentgenol. 1980; 134: 979-983.
25. Shanahan TK, Logemann JA, Rademaker AW, Pauloski BR, Kahrilas PJ. Chin-down posture effect on aspiration in dysphagic patients. Arch Phys Med Rehabil. 1993; 74: 736-739.
26. Rasley A, Logemann JA, Kahrilas PJ, Rademaker AW, Pauloski BR, Dodds WJ. Prevention of barium aspiration during videofluoroscopic swallowing studies: Value of change in posture. Am J Roentgenol. 1993; 160: 1005-1009.
27. Channer KS, Virjee J. Effect of posture and drink volume on the swallowing of capsules. Br Med J. 1982; 285: 1702.
28. McFarland DH, Lund JP, Gagner M. Effects of posture on the coordination of respiration and swallowing. J Neurophysiol. 1994; 72: 2431-2437.
29. Tsukada T, Taniguchi H, Ootaki S, Yamada Y, Inoue M. Effects of food texture and head posture on oropharyngeal swallowing. J Appl Physiol. 2009; 106: 1848-1857.
30. Logemann JA, Rademaker AW, Pauloski BR, Kahrilas PJ. Effects of postural change on aspiration in head and neck surgical patients. Otolaryngol Head Neck Surg. 1994; 110: 222-227.
31. Ekberg O. Closure of the laryngeal vestibule during deglutition. Acta Otolaryngol. 1982; 93: 123-129.
32. Leigh JH, Cho K, Barcenas CL, Paik NJ. Dysphagia Aggravated by cervical hyperlordosis. Am J Phys Med Rehabil. 2011; 90: 704.
33. Guo GM, Li J, Diao QX, Zhu TH, Song ZX, Guo YY, et al. Cervical lordosis in asymptomatic individuals: A meta-analysis. J Orthop Surg Res. 2018; 13: 147.

34. Chen Y, Luo J, Pan Z, Yu L, Pang L, Zhong J, et al. The change of cervical spine alignment along with aging in asymptomatic population: A preliminary analysis. Eur Spine J. 2017; 26: 2363-2371.
35. Attiah M, Gaonkar B, Alkhalid Y, Villaroman D, Medina R, Ahn C, et al. Natural history of the aging spine: A cross-sectional analysis of spinopelvic parameters in the asymptomatic population. J Neurosurg Spine. 2019; 32: 63-68.
36. Kim HJ, Lenke LG, Oshima Y, Chuntarapas T, Mesfin A, Hershman S, et al. Cervical lordosis actually increases with aging and progressive degeneration in spinal deformity patients. Spine Deform. 2014; 2: 410-414.
37. Tang R, Ye IB, Cheung ZB, Kim JS, Cho SK-W. Age-related Changes in Cervical Sagittal Alignment: A Radiographic Analysis. Spine. 2019; 44: E1144-E1150.
38. Harrison DE, Harrison DD, Cailliet R, Troyanovich SJ, Janik TJ, Holland B. Cobb method or Harrison posterior tangent method: Which to choose for lateral cervical radiographic analysis. Spine. 2000; 25: 2072-2078.
39. Tanure MC, Pinheiro AP, Oliveira AS. Reliability assessment of Cobb angle measurements using manual and digital methods. Spine J. 2010; 10: 769-774.
40. Brates D, Steele C, Molfenter SM. Measuring hyoid excursion across the life span: Anatomical scaling to control for variation. J Speech Lang Hear Res. 2020; 63: 125-134.
41. Steele CM, Peladeau-Pigeon M, Barbon CAE, Guida BT, Namasivayam-MacDonald AM, Nascimento WV, et al. Reference values for healthy swallowing across the range from thin to extremely thick liquids. J Speech Lang Hear Res. 2019; 62: 1338-1363.
42. Molfenter SM, Steele CM. The relationship between residue and aspiration on the subsequent swallow: an application of the normalized residue ratio scale. Dysphagia. 2013; 28: 494-500.
43. Pearson WG, Molfenter SM, Smith ZM, Steele CM. Image-based measurement of post-swallow residue: The normalized residue ratio scale. Dysphagia. 2013; 28: 167-177.
44. Stokely SL, Peladeau-Pigeon M, Leigh C, Molfenter SM, Steele CM. The relationship between pharyngeal constriction and post-swallow residue. Dysphagia. 2015; 30: 349-356.
45. Molfenter SM, Steele CM. Use of an anatomical scalar to control for sex-based size differences in measures of hyoid excursion during swallowing. J Speech Lang Hear Res. 2014; 57: 768-778.
46. Fleiss JL. Design and analysis of clinical experiments. John Wiley & Sons; 2011.
47. Kotrlik J, Williams H. The incorporation of effect size in information technology, learning, information technology, learning, and performance research and performance research. Inform Technol Learn Perform J. 2003; 21: 1.
48. Friedenberg ZB, Edeiken J, Spencer HN, Tolentino SC. Degenerative changes in the cervical spine. JBJS. 1959; 41: 61-102.


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Review

# A Delirium Monitoring Program for Hospitalized Older Adults: An Approach to Age-Friendly Health Systems

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**Abstract**

Delirium is an acute change in mental status with key features of inattention and disorganized thinking. It is particularly common in older adults, with multiple and varied causes. Delirium increases the risk of morbidity, mortality, institutionalization, and healthcare costs; however, it is often missed because it is difficult to recognize without the use of a validated screening tool. The Age-Friendly Health Systems (AFHS) initiative highlights the need for implementation of a delirium monitoring program in hospitals through early identification, using delirium screening tools and the non-pharmacological approach to prevent and treat delirium. Implementing a delirium monitoring program requires leadership engagement, multidisciplinary team involvement, staff education and training, proper documentation and communication, electronic medical records integration, and addressing identified barriers to success. This review will discuss 1) the impact of delirium in hospitalized older adults, 2) the guidelines of AFHS in establishing delirium monitoring programs, and 3) a practical approach to implementing a delirium program with a focus on screening and treatment.

**Keywords**
Delirium; screening; implementation; age-friendly health systems; older adults; geriatrics; hospital care; acute care

## 1. Case Vignette

A 76-year-old female presents for admission to the hospital for a diagnosis of community-acquired pneumonia. She has a history of essential hypertension and mild Alzheimer's type dementia. She lives with her daughter but performs all activities of daily living (ADLs) independently. Upon admission, she is alert and oriented x 4 and able to follow commands but is mildly hypoxic with oxygen saturation of 90%. The rest of her physical exam is otherwise normal. She is treated with oxygen and antibiotics. On day 2 of hospitalization, her daughter notes that since admission the patient is sleeping more, not eating her meals, and does not answer questions appropriately. On exam, she is now disheveled and mumbling, arousable but quickly falls back asleep, and is oriented to person only.

A review of her medications did not reveal any sedatives or other possible offending medications. She however was noted to be missing her eyeglasses and had been in bed since admission. After an extensive work-up, which included unremarkable labs and imaging of her chest and brain, a diagnosis of delirium was made, and non-pharmacological delirium treatment protocols were initiated. By day 5 of hospitalization, the patient is alert and oriented x 4 again and able to follow commands, although sleeping more than usual and not being mobilized. Her daughter also notes that the patient seems to struggle with knitting, which has been her favorite hobby for years. She was discharged to a skilled nursing facility for rehabilitation.

What was wrong with this patient? Could this have been prevented? Could this have been identified earlier? How would you care for this patient?

## 2. Introduction

This case illustrates an all too common experience for older adults in the hospital setting - delirium. Delirium is an acute or fluctuating alteration in mental status characterized by inattention, altered level of consciousness, and disorganized thinking [1, 2]. Patients may arrive to the hospital with delirium, but often delirium develops over the course of a hospitalization and is now the leading hospital-acquired complication for older adults [2, 3]. The etiology of delirium is usually multifactorial due to an interaction of predisposing and precipitating factors [4]. Delirium is associated with prolonged hospitalization, discharge to settings other than home, and mortality [5]. Additionally, ongoing research has shown that even after the most severe symptoms have resolved, prolonged cognitive impairment may plague patients for years [6-8].

Like many geriatric syndromes, delirium is often preventable but underdiagnosed. Without use of a validated screening tool, 75% of delirium cases may be missed [6]. When a system-wide approach is applied to prevent, detect, and manage delirium, improved patient outcomes can be accomplished [9]. Recently, a social movement was developed, known as Age-Friendly Health systems (AFHS), which advocates for delirium monitoring programs at hospitals, for all older adults (>65 years old). AFHS encourages that hospitals set up initiatives to prevent, identify, and manage delirium.

This paper will discuss 1) the impact of delirium in hospitalized older adults, 2) the guidelines of AFHS in establishing delirium monitoring programs, and 3) a practical approach to implementing a delirium program with a focus on screening and treatment.

### *2.1 Clinical and Public Health Impact of Delirium*

Delirium is very common in the hospital setting, affecting up to 20-40% of older adults on medical and surgical units, and 70-75% in the intensive care setting [8, 10-12]. Although often not considered with the seriousness of other organ failure, such as heart failure or renal failure, "brain failure," as delirium has been colloquially referred to, is potentially a life-threatening condition. In fact, older adults with delirium have been found to have a mortality rate comparable to acute myocardial infarction [13]. Patients who develop delirium have much poorer outcomes compared to similar patients that do not. Delirium is an independent risk factor for mortality. In-hospital mortality rates have been as high as 25-33%, and risk of death remains increased up to 2 years later in those that survive hospitalization [5]. Delirium increases risk for falls, infections, prolonged mechanical ventilation, and functional decline, resulting in loss of independence, depression, post-traumatic stress disorder, and long-term cognitive impairment [5, 6]. Also, patients who become delirious in the hospital are more likely to be discharged to a nursing facility rather than home [5]. Due to the above factors, delirium is extremely costly to the health care system. Costs related to delirium in the United States have been estimated to be $164 billion per year, which nearly matches the cost of diabetes care and complications [14].

### *2.2 Age-Friendly Health Systems*

The population of older adults aged 65 years and over in the United States is rapidly growing [15]. This population often requires highly complex health care, posing a great challenge and burden for the current health system [16]. Older adults are at increased risk of developing delirium and its serious consequences due to higher prevalence of predisposing risk factors (e.g. older age, functional impairment, vision impairment, hearing impairment) [4]. Furthermore, frailty in older adults also increases the risk of delirium, due to increased vulnerability and decreased adaptation to stressors [17, 18]. In order to address this, the Institute for Healthcare Improvement (IHI) and the John A. Hartford Foundation partnered with the American Hospital and Catholic Health Associations in 2017 to develop an initiative titled "Age-Friendly Health Systems" [19-21]. This initiative focuses on using the "4Ms framework" to assess and address the multidimensional health care needs of older adults, tailored to their goals, with the aim of improving outcomes. The components of the 4Ms-medication, mentation, mobility, and what matters most-are evidence-based and designed to be implemented together across all care settings (Figure 1). The implementation of this framework has also been shown to provide financial benefits to health systems, with one health system estimating an annual net income potential of $3 million [22]. The mentation component of the 4Ms involves the prevention, identification, and management of delirium in hospitalized older adults, and depression and dementia in outpatients [21].

For delirium, the key actions of age-friendly hospitals are to use non-pharmacologic means to prevent and treat delirium (such as hearing aids, glasses, ensuring oral hydration/nutrition) and screening for delirium at least every 12 hours [21]. In this paper, while we will touch on

prevention, screening, and management, we will focus on the key steps needed to implement a delirium monitoring program.

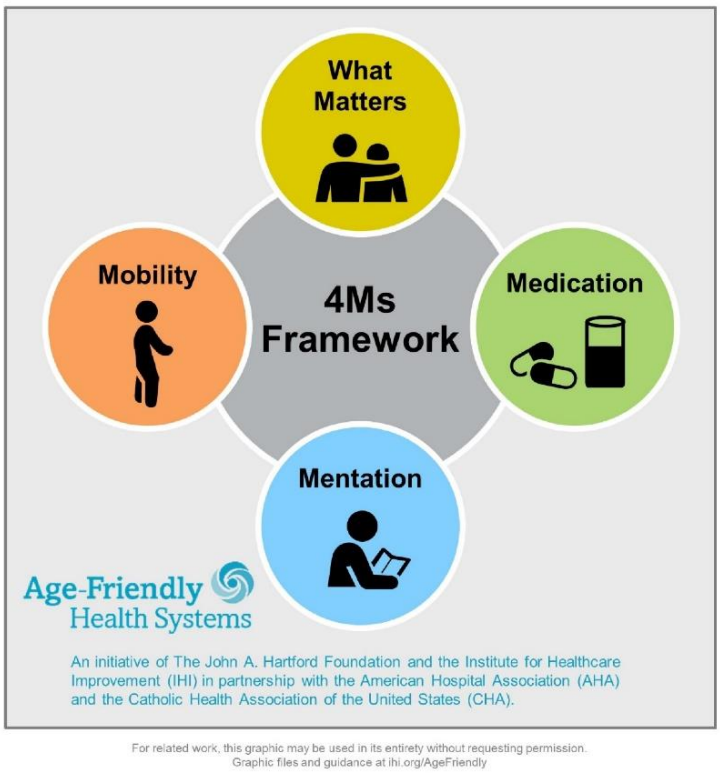


**Figure 1** 4Ms Framework for Age-Friendly Health Systems. The Institute for Healthcare Improvement and its partners established the 4Ms framework as a process for providing evidence-based, age-friendly healthcare across a health system. Screening hospitalized older adults for delirium at least every 12 hours is a key action of an age-friendly health system [21]. www.ihi.org/engage/initiatives/age-friendly-health-systems.

## 3. Delirium Prevention

Delirium can occur in any hospitalized older adult, however some populations considered high risk are patients with advanced age, dementia, infections, multimorbidity, high illness severity, prolonged hospital stay, decreased mobility, sensory impairments, dehydration, electrolyte disturbances, urinary catheterization, malnutrition and those on potentially inappropriate medications [23, 24]. This population should be targeted for early screening and prevention of delirium. Up to 40% of delirium is preventable by non-pharmacologic means [25, 26]. Hence, delirium prevention should be based on a non-pharmacological approach [9]. The Hospital Elder Life Program (HELP) has robust evidence demonstrating its effectiveness in preventing delirium using a non-pharmacologic approach [25]. The main components of HELP are included in the recommendations by AFHS for preventing delirium:

- Ensure proper oral hydration and nutrition, as well as trying to eliminate intravenous fluids/medications/nutrition if possible.
- Reorient often, with help from family members.

- Modify the environment by ensuring blinds are open during the day, minimize use of tethering devices.
- Restore sensory mechanisms, such as ensuring eyeglasses and hearing aids are in use.
- Ensure good pain control by having a high index of suspicion and assessing for pain, scheduling pain medications and using non-opioid analgesics.
- Encourage mobility.
- A protocol to minimize sleep disruption, such as the use of earplugs, sleeping masks and reducing nighttime vital signs, should also be put in place [21].

The mnemonic HOMMEEESS can be a helpful way to remember delirium prevention strategies (Figures 2 and 3), and the individual components of this guide are based on the HELP and AFHS recommendations [21, 25]. The Acute Care for the Elderly (ACE) unit is appropriately modeled to allow implementation of these strategies; however, these can also be implemented on a general medical/surgical floor with proper staff training. Pharmacists could also help with medication reconciliation and reduction of deliriogenic medication use (Figure 4). In patients who are admitted to a non-geriatric primary service, early and proactive geriatrics consultation should be placed in order to prevent delirium in patients at high risk [26]. These high risk patients may be identified using the AWOL screening tool, which has been validated to predict the risk of development of delirium in hospitalized patients [27].

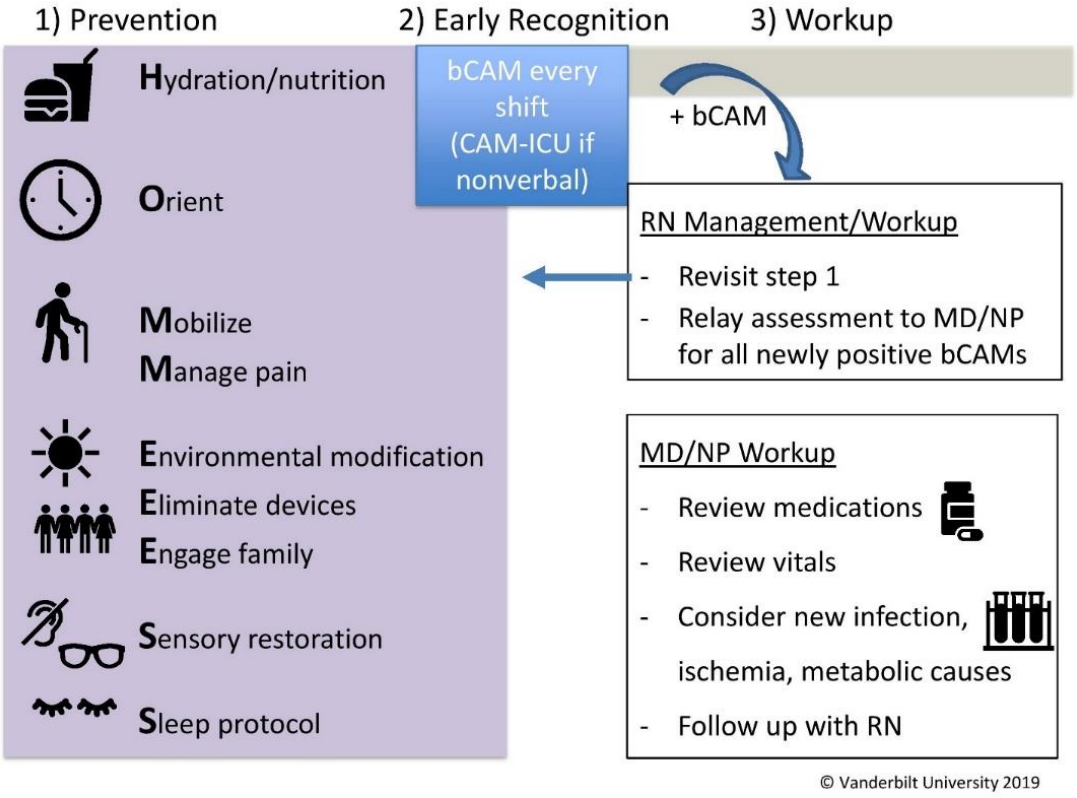


**Figure 2** Delirium Care - Nursing Guide. Example of a nursing-focused framework for delirium prevention and screening in the non-ICU hospital setting. bCAM - brief confusion assessment method; CAM-ICU - confusion assessment method for the intensive care unit; MD - medical doctor; NP - nurse practitioner; RN-registered nurse. The evidence for the reliability and validity of HOMMEEESS as a guide is yet to be determined.

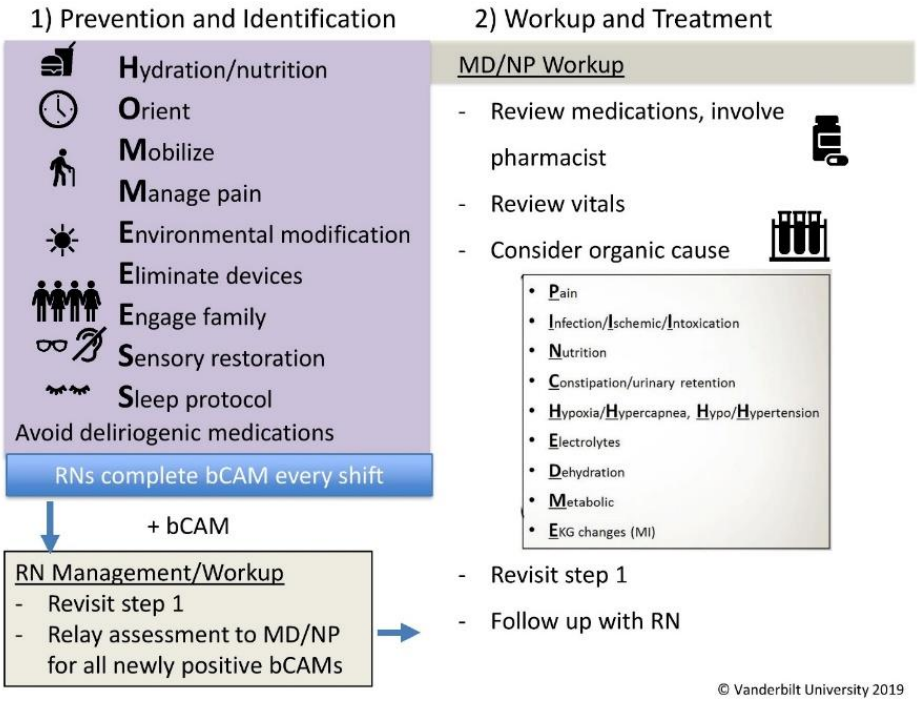


**Figure 3** Delirium Care-Provider Guide. Example of a provider-focused framework for delirium prevention, evaluation and treatment in the non-ICU hospital setting. bCAM - brief confusion assessment method; MD - medical doctor; NP - nurse practitioner; RN - registered nurse; MI - myocardial infarction. The evidence for the reliability and validity of HOMMEEESS as a guide is yet to be determined.

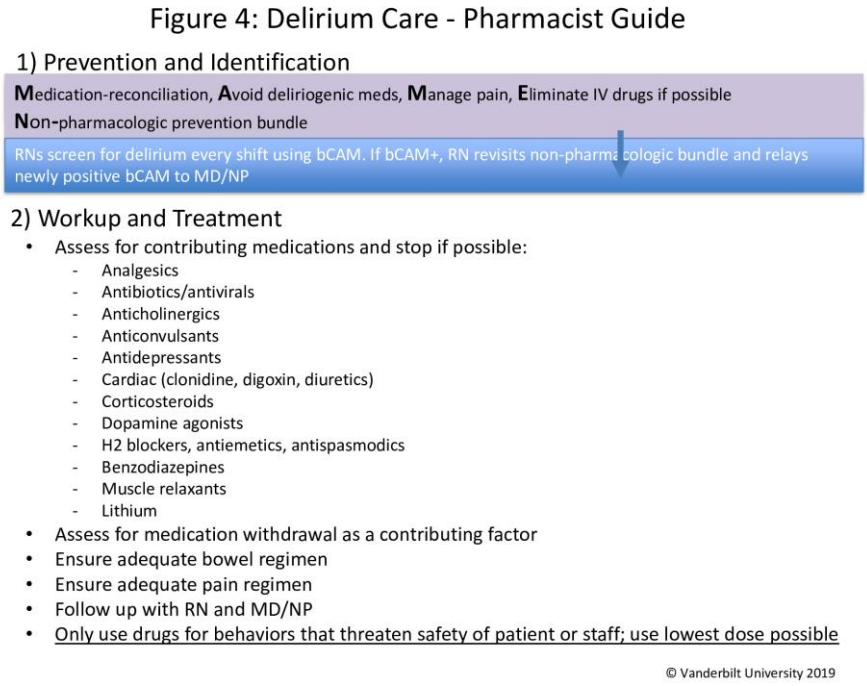


**Figure 4** Delirium Care-Pharmacist Guide. Example of a pharmacist-focused framework for delirium prevention, evaluation and treatment in the non-ICU hospital setting. bCAM - brief confusion assessment method; MD - medical doctor; NP - nurse practitioner; RN - registered nurse; IV - intravenous.

## 4. Delirium Screening

Screening for delirium every 12 hours is recommended by the AFHS and is already recognized as a hospital standard for older surgical patients [28]. The science of delirium screening has advanced rapidly, with many screening tools now available.

### *4.1 Delirium Screening Tools*

The diagnosis of delirium is often missed without the use of a structured diagnostic tool for rapid and accurate screening [6, 29]. Multiple screening tools have been validated over the years [30]. The Confusion Assessment Method (CAM) is one of the most valid and reliable tools for detecting delirium and uses the four feature structure to assess delirium-1) acute change or fluctuation in mental status from baseline, 2) inattention, 3) altered level of consciousness, and 4) disorganized thinking [31, 32]. A patient is considered CAM positive (i.e. delirium present) if features 1 and 2 and either feature 3 or 4 are present. Many derivations of the CAM have been developed for special populations. For example, in the intensive care unit (ICU), the Confusion Assessment Method for the ICU (CAM-ICU) is an accepted and widely used delirium screening tool [33, 34]. Similarly, a modified version of the CAM-ICU called the brief Confusion Assessment Method (bCAM) was developed for use in busy non-critical care settings and can be quickly and reliably performed by non-physicians [35]. The bCAM takes less than two minutes to perform and assesses the four features in the CAM [30, 36]. Figure 5 shows the bCAM algorithm and details how each feature can be assessed. Features 1 and 2 and either Feature 3 or 4 most be present in order to be considered bCAM positive, and thus highly suggestive of delirium [30]. AFHS also recommends the CAM, CAM-ICU and bCAM as some of the many valid delirium tools to implement [21].

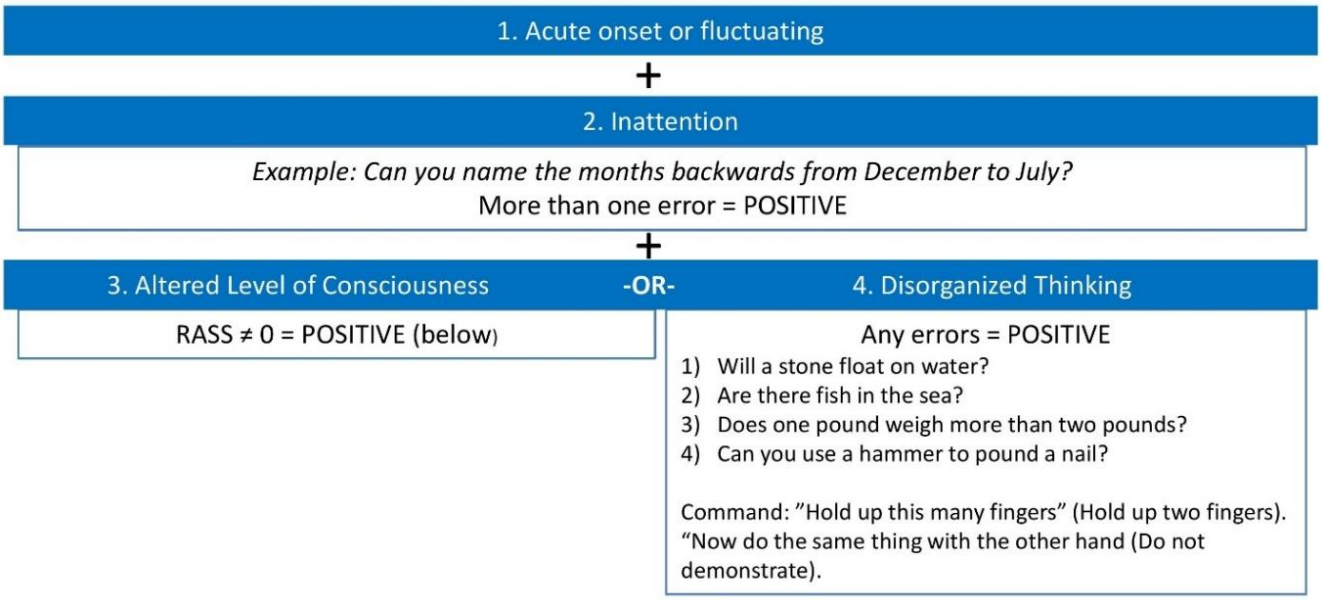


**Figure 5** Brief Confusion Assessment Method (bCAM). Features of the brief Confusion Assessment Method (bCAM), which is a validated delirium screening tool. bCAM positive = Features 1+2+(3 or 4) = Delirium. RASS - Richmond Agitation and Sedation Scale.

The efficacy of delirium screening tools in the clinical setting has been well studied. The CAM was shown to be 94-100% sensitive and 90-95% specific when compared to a psychiatrist's assessment in the original validation study [31]. A systematic review and meta-analysis of prospective studies conducted in hospitalized patients showed a pooled sensitivity of 86% and pooled specificity of 93% [29]. The efficacy of the CAM-ICU was examined in two systematic reviews and meta-analyses, with both studies showing a pooled sensitivity of 74% and 80% respectively, and a pooled specificity of 96% [34, 37]. In another study, the bCAM was found to be 84% sensitive and 96% specific when performed by physicians in the emergency department [38]. The specificity of the bCAM was similar when performed by non-physicians (97%), however, the sensitivity was lower at 78% [38]. A modified version of the bCAM was later assessed in a secondary analysis, showing improved sensitivity of 82% when performed by non-physicians, and similar results for physicians [35]. A recent study in hospitalized palliative care patients also showed good sensitivity and specificity of the bCAM at 80% and 87% respectively [39]. There have also been other studies of delirium screening using the CAM-ICU in both the non-ICU and ICU settings that although showed lower sensitivities, consistently demonstrated high specificities [30]. This highlights a limitation of delirium screening tools like the CAM-ICU or bCAM that may give some false negative results, thus missing some delirious patients. However, the low false positive rates of these tools do give a clinician more confidence that delirium is truly present with a positive screen. Overall, the highlighted studies have shown that the bCAM can be used to efficiently screen for and detect delirium by both physicians and non-physicians.

### *4.2 Implementing Delirium Screening on an Acute Care for the Elderly Unit*

The ACE Unit is an inpatient floor unit designed for the hospitalization of older adults aged 65 and over. This unit is designed as a continuous quality improvement care model focused on preserving the functional independence of older adults and improving outcomes by using multi-dimensional interventions [40]. Implementation of delirium screening on the ACE unit is in line with the goals of the unit and is important to allow prevention, early identification, and management of delirium [30]. Although we specify implementation strategies on the ACE unit, these can also be applied to a general medical/surgical floor, with appropriate staff training.

The goal of delirium screening should be to integrate the process into routine daily care [21]. Various studies have shown the possibility of successful implementation of delirium screening using different screening tools and strategies [30]. One study focused on the training of nurses in the correct use of the CAM-ICU to assess delirium every 8 hours, using lectures, videos and bedside application [41]. A different study confirmed that the use of these educational methods improved the rates of delirium screening by nurses when incorporated into standard daily nursing practice [42]. In addition to education, the standardization of delirium screening documentation and communication of delirium status to clinicians increases delirium screening by dayshift nurses to as high as 93% [43]. An implementation strategy used in another study focused on identifying probable barriers and facilitators for screening via medical staff interviews, resulting in significantly improved screening, from 77% to 92% [44]. This strategy allowed them to address the identified barriers using facilitators, for example, integrating the screening tool into the patient data management system, as well as, obtaining support from senior nurses and nursing leadership [44].

There is paucity of data on delirium implementation strategies on the ACE unit, however more data is available in the ICU, and these can be adapted for use on the ACE unit, given the feasibility and success of these strategies. Figure 6 shows an outline of steps and strategies that may be used to implement delirium screening on the ACE unit, using the bCAM as a screening tool. Engaging stakeholders, such as nursing and physician leadership to get buy-in is an important step for successful implementation, after which an interdisciplinary team should be created [30]. This team should consist of physicians, nurse practitioners, nurses, pharmacists, therapists, unit leadership, ancillary staff, as well as patient/family representatives, who could help drive the implementation process. Education and training of nurses and clinicians should focus on knowledge about delirium and the bCAM, as well as bedside applications [30]. The need to assess accuracy of screening, proper documentation, and communication with clinicians should be emphasized. The electronic medical record should be designed to allow easy documentation of bCAM results at every shift, which not only enhances communication but also allows easy daily data collection for analysis [30]. Data should be analyzed regularly, and results communicated to staff and other members of the interdisciplinary team at regular meetings, perhaps monthly. Barriers to delirium screening should be identified, addressed, and reassessed continuously. Throughout the implementation process, it should be noted that education and training may need to be repeated for new staff and reinforced for current staff [30].

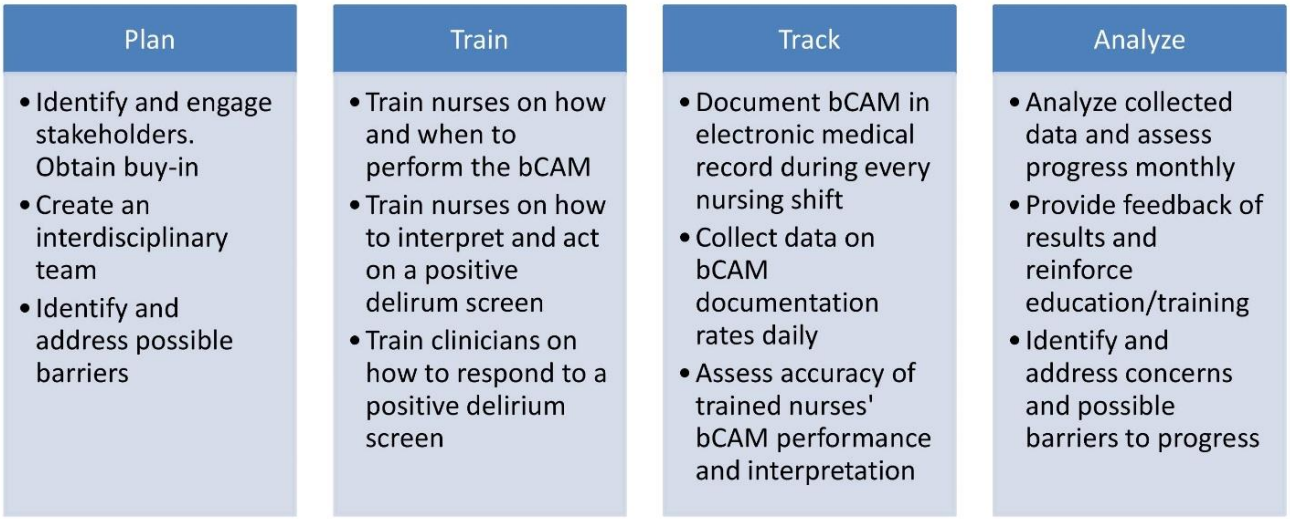


**Figure 6** Implementation of Delirium Screening Using the Brief Confusion Assessment Method (bCAM). Example of steps involved in implementation of the bCAM as a delirium screening tool on an inpatient unit, with emphasis on buy-in, interdisciplinary teamwork, education, training and communication. These strategies are necessary to achieve successful implementation. bCAM - brief confusion assessment method.

## 5. Delirium Management: Evaluation and Treatment

Delirium screening implementation can be discouraging if care teams do not intervene when there is a positive delirium screen [45]. Hence, care teams need to work closely together not only to prevent and detect delirium early but also to evaluate for possible delirium triggers and provide the appropriate treatment. While all members of the interdisciplinary team are important in

optimizing outcomes for patients with delirium, three key players in this process are the nurses, clinicians/providers, and pharmacists who should work together to achieve this goal. Figures 2-4 illustrate each key player's role in the prevention, early identification, evaluation, and treatment of delirium. Family member integration into this care model has also shown improved outcomes [3, 46].

### *5.1 Evaluation*

The diagnosis of delirium should trigger a prompt and thorough evaluation to identify reversible causes of delirium [3]. The first step is for nursing staff to feel empowered to quickly communicate the positive bCAM screen to clinicians, and while awaiting this evaluation, revisit the delirium prevention strategies and address any possible predisposing factors. The clinician evaluation should include a thorough history and physical exam, focusing on new symptoms, medication review (with the help of the pharmacist), vital signs, lung exam and neurologic exam [3]. Some organic causes of delirium include pain, infection (urinary tract infection, pneumonia), ischemia, constipation/urinary retention, dehydration and electrolyte derangements. The mnemonic PINCHEDME can be a helpful way to remember delirium etiology (Figure 3). The causes of delirium are frequently multifactorial, and laboratory testing/imaging should be guided by history and physical exam.

### *5.2 Treatment*

It is important to address factors contributing to delirium that have been identified during the evaluation early on, in order to reduce poor outcomes from delirium [30]. This step requires proper integration within the care team. The mainstay of treatment should be focused on non-pharmacologic interventions such as reorientation, ensuring water and oral fluids are easily accessible, providing an adequate pain regimen, modifying the environment, restoring sensory mechanisms, minimizing sleep disruption, encouraging mobility, removing tethering devices, avoiding restraints, and stopping/tapering off all offending medications [21]. Pharmacologic treatment should be targeted at the underlying etiology, such as the use of laxatives for constipation and antibiotics for infections. The use of sedating medications should generally be avoided, particularly the use of benzodiazepines, which have been shown to worsen delirium [47]. In challenging cases, benzodiazepine use should be limited to delirium due to alcohol or benzodiazepine withdrawal if possible [3]. Medications used to treat behavioral disturbances, such as antipsychotics, should also be avoided and only used for behavior that threaten safety of the patient or staff [30]. When needed, the lowest dose possible should be used, for the shortest duration that is necessary [3]. Studies have shown no benefit with the use of antipsychotics otherwise [48, 49].

## 6. Conclusions and Recommendations

The patient in this vignette had a diagnosis of delirium evidenced by her change in mental status from baseline, inattention, and altered level of consciousness. This may have been identified earlier if delirium screening during every shift was done using a validated screening tool. Furthermore, this scenario may have been prevented if delirium prevention strategies such as

reorientation, early mobilization and restoration of sensory mechanisms were already in place on the unit. Although her delirium resolved with appropriate non-pharmacological delirium treatment, she now has a decline in her functional status and requires post-acute care for rehabilitation. This case highlights some adverse outcomes of delirium and emphasizes the importance of delirium screening in hospitalized older adults. Implementation of delirium screening using a validated tool addresses the mentation component of the 4Ms and incorporates delirium prevention, detection, evaluation, and management into the plan of care-a step towards becoming an age-friendly health system.

**Author Contributions**

Study concept and design: TA, JP, MCD; Acquisition of subjects and/or data: TA; Analysis and interpretation of data: TA, JP, MCD; Preparation of manuscript: TA, JP, MCD.

**Competing Interests**

The authors have declared that no competing interests exist.

**References**

1. Edition F. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. Hshieh TT, Inouye SK, Oh ES. Delirium in the elderly. Clin Geriatr Med. 2020; 36: 183-199.
3. Marcantonio ER. Delirium in hospitalized older adults. N Engl J Med. 2017; 377: 1456-1466.
4. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet. 2014; 383: 911-922.
5. Witlox J, Eurelings LSM, Jonghe JFM de, Kalisvaart KJ, Eikelenboom P, Van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: A meta-analysis. JAMA. 2010; 304: 443-451.
6. Inouye SK, Marcantonio ER, Kosar CM, Tommet D, Schmitt EM, Travison TG, et al. The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. Alzheimers Dement. 2016; 12: 766-775.
7. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012; 367: 30-39.
8. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013; 369: 1306-1316.
9. Hshieh TT, Yue J, Oh E, Puelle M, Dowal S, Travison T, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: A meta-analysis. JAMA Intern Med. 2015; 175: 512-520.
10. Francis J. Delirium in older patients. J Am Geriatr Soc. 1992; 40: 829-838.
11. Schubert M, Schürch R, Boettger S, Garcia Nuñez D, Schwarz U, Bettex D, et al. A hospital-wide evaluation of delirium prevalence and outcomes in acute care patients-a cohort study. BMC Health Serv Res. 2018 ;18: 550.
12. McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: Occurrence and clinical course in older patients. J Am Geriatr Soc. 2003; 51: 591-598.

13. Gower LEJ, Gatewood MO, Kang CS. Emergency department management of delirium in the elderly. West J Emerg Med. 2012; 13: 194-201.
14. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008; 168: 27-32.
15. National institute on aging. Introduction [Internet]. National institute on aging. 2020 [cited 2020 Apr 10]. Available from: https://www.nia.nih.gov/living-long-well-21st-century-strategic-directions-research-aging/introduction
16. Kennedy T. Strength in age-friendly health systems: An innovative integrated interprofessional model. Innov Aging. 2019; 3: S829.
17. Eeles EMP, White SV, O'Mahony SM, Bayer AJ, Hubbard RE. The impact of frailty and delirium on mortality in older inpatients. Age Ageing. 2012; 41: 412-416.
18. Walston J. Frailty research moves beyond risk assessment. J Gerontol A Biol Sci Med Sci. 2017; 72: 915-916.
19. Fulmer T, Mate KS, Berman A. The age-friendly health system imperative. J Am Geriatr Soc. 2018; 66: 22-24.
20. Mate KS, Berman A, Laderman M, Kabcenell A, Fulmer T. Creating age-friendly health systems-A vision for better care of older adults. Healthc (Amst). 2018; 6: 4-6.
21. IHI. Age-friendly health systems: Guide to using the 4ms in the care of older adults [Internet]. Institute for healthcare improvement; 2019 [cited 2020 Apr 9]. Available from: http://www.ihi.org/Engage/Initiatives/Age-Friendly-Health-Systems/Documents/IHIAgeFriendlyHealthSystems_GuidetoUsing4MsCare.pdf
22. IHI. The business case for becoming an age-friendly health system [Internet]. Institute for healthcare improvement; 2019 [cited 2020 Jun 29]. Available from: http://www.ihi.org/Engage/Initiatives/Age-Friendly-Health-Systems/Documents/IHI_Business_Case_for_Becoming_Age_Friendly_Health_System.pdf
23. Vasilevskis EE, Han JH, Hughes CG, Ely EW. Epidemiology and risk factors for delirium across hospital settings. Best Pract Res Clin Anaesthesiol. 2012; 26: 277-287.
24. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical units: A systematic review and meta-analysis. Age Ageing. 2014; 43: 326-333.
25. Inouye SK, Bogardus ST, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999; 340: 669-676.
26. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: A randomized trial. J Am Geriatr Soc. 2001; 49: 516-522.
27. Douglas VC, Hessler CS, Dhaliwal G, Betjemann JP, Fukuda KA, Alameddine LR, et al. The AWOL tool: Derivation and validation of a delirium prediction rule. J Hosp Med. 2013; 8: 493-499.
28. Koebrugge B, Koek HL, van Wensen RJA, Dautzenberg PLJ, Bosscha K. Delirium after abdominal surgery at a surgical ward with a high standard of delirium care: Incidence, risk factors and outcomes. Dig Surg. 2009; 26: 63-68.
29. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: Value of bedside instruments. JAMA. 2010; 304: 779-786.

30. Brummel NE, Vasilevskis EE, Han JH, Boehm L, Pun BT, Ely EW. Implementing delirium screening in the intensive care unit: Secrets to success. Crit Care Med. 2013; 41: 2196-2208.
31. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: The confusion assessment method: A new method for detection of delirium. Ann Intern Med. 1990; 113: 941-948.
32. Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The confusion assessment method (CAM): A systematic review of current usage. J Am Geriatr Soc. 2008; 56: 823-830.
33. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001; 286: 2703-2710.
34. Gusmao-Flores D, Salluh JIF, Chalhub RÁ, Quarantini LC. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: A systematic review and meta-analysis of clinical studies. Crit Care. 2012; 16: R115.
35. Han JH, Wilson A, Graves AJ, Shintani A, Schnelle JF, Ely EW. A quick and easy delirium assessment for non-physician research personnel. Am J Emerg Med. 2016; 34: 1031-1036.
36. Adult Non-ICU Care: Monitoring Delirium [Internet]. [cited 2020 Apr 10]. Available from: https://www.icudelirium.org/medical-professionals/adult-non-icu-care-monitoring-delirium
37. Neto AS, Nassar AP, Cardoso SO, Manetta JA, Pereira VGM, Espósito DC, et al. Delirium screening in critically ill patients: A systematic review and meta-analysis. Crit Care Med. 2012; 40: 1946-1951.
38. Han JH, Wilson A, Vasilevskis EE, Shintani A, Schnelle JF, Dittus RS, et al. Diagnosing delirium in older emergency department patients: Validity and reliability of the delirium triage screen and the brief confusion assessment method. Ann Emerg Med. 2013; 62: 457-465.
39. Wilson JE, Boehm L, Samuels LR, Unger D, Leonard M, Roumie C, et al. Use of the brief confusion assessment method in a veteran palliative care population: A pilot validation study. Palliat Support Care. 2019; 17: 569-573.
40. Palmer RM. the acute care for elders unit model of care. Geriatrics (Basel). 2018; 3: 59.
41. Souza R, Bersaneti M, Siqueira E, Meira L, Brumatti D, Prado N. Nurses' training in the use of a delirium screening tool [Internet]. 2017 [cited 2020 Apr 10]. Available from: http://www.scielo.br/scielo.php?pid=S1983-14472017000100801&script=sci_arttext&tlng=en
42. Scott P, McIlveney F, Mallice M. Implementation of a validated delirium assessment tool in critically ill adults. Intensive Crit Care Nurs. 2013; 29: 96-102.
43. Aparanji K, Kulkarni S, Metzke M, Schmudde Y, White P, Jaeger C. Quality improvement of delirium status communication and documentation for intensive care unit patients during daily multidisciplinary rounds. BMJ Open Qual. 2018; 7: e000239.
44. van den Boogaard M, Pickkers P, van der Hoeven H, Roodbol G, van Achterberg T, Schoonhoven L. Implementation of a delirium assessment tool in the ICU can influence haloperidol use. Critical Care. 2009; 13: R131.
45. Pun BT, Gordon SM, Peterson JF, Shintani AK, Jackson JC, Foss J, et al. Large-scale implementation of sedation and delirium monitoring in the intensive care unit: A report from two medical centers. Crit Care Med. 2005; 33: 1199-1205.

46. Cotton D, Taichman D, Williams S, Marcantonio ER. Delirium. Ann Intern Med. 2011; 154: ITC6-1.
47. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006; 104: 21-26.
48. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: A systematic review and meta-analysis. J Am Geriatr Soc. 2016; 64: 705-714.
49. Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, et al. Haloperidol and ziprasidone for treatment of delirium in critical illness. N Engl J Med. 2018; 379: 2506-2516.

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Review

# Ageing, Comorbidity and Frailty-Synergistic Risk Factors for Covid-19 Adverse Outcomes

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**Abstract**

With life-expectancy rising globally, the prevalence of ageing, comorbidity and frailty is likely to increase especially in the low and middle income countries. The emergence of the new COVID-19 pandemic has been concentrated in this group of patients and has led to worse outcomes compared to younger and less comorbid populations. This group of patients is at an increased risk of multi-organ consequences of systemic disease. Therefore, systemic assessment of these patients from the outset and optimisation of their pre-existing conditions in addition to the treatment of COVID-19, is required to reduce the risk of multi-organ failure. Decisions regarding escalation of treatment should include frailty assessment along with the overall comorbid condition and function. The expected projection of the ageing population will mean the population is increasingly at risk, locally and globally, of managing a new pandemic, in particular in those low and middle income countries with less access to healthcare resources. Therefore, WHO and governments around the world must consider this potential threat in future health care planning.

**Keywords**
COVID-19; frailty; comorbidity; ageing; outcome

## 1. Introduction

The global population is ageing. With this, the risk of infections increases. In December 2019, a pneumonia-like illness was first reported in Wuhan-China caused by a new coronavirus - corona virus disease-2019 (COVID-19) - which has since caused a global pandemic [1]. The incidence, severity and mortality of COVID-19 infection appears to be shifted towards old age, especially in those who are frail and with multiple comorbidities. The most commonly reported comorbid conditions are hypertension, cardiovascular disease, respiratory disease and diabetes mellitus, all of which are more prevalent in older age [2]. Although frailty has not been formally assessed in most COVID-19 published literature, it is possible that frailty was the surrogate marker of old age and the associated comorbidities. Frailty is characterised by dysregulation in the innate and adaptive immunity that leads to increased susceptibility to severe infections. This manuscript reviews the published data on COVID-19 infection and explores the synergistic role of ageing and frailty in increasing the risk of adverse outcomes.

## 2. Aging

Globally, people are living longer. By the year 2050, the number of people aged ≥60 years is expected to reach 2 billion, a surge from a reported 900 million people in 2015. People ≥80 years are the fastest growing group and will almost quadruple to reach 434 million in 2050 from the current 125 million [3]. The pace of population ageing worldwide is also increasing dramatically. While this demographic shift towards old age, known as population ageing, initially started in high-income countries such as Japan (currently 30% of the population is already over 60 years old), it is now moving fast towards low- and middle-income countries and in 2050, 80% of all older people are expected to be living in these countries [3].

There is, however, little evidence to suggest that older people today are experiencing their later years in better health than their parents. Although over the last 30 years, the rates of severe disability may have been reduced, there has been no significant change in mild to moderate disability over the same period. In addition to the expected increase in life expectancy, this will be associated with increased prevalence of comorbidity.

## 3. Comorbidity

Patients naturally accumulate comorbidity with increased age and population studies have previously suggested that 31.4% of those over 85 years will have four or more chronic conditions [4]. Furthermore, there is likely to be a development of subclinical pathology in various organ systems, even in the absence of overt disease, which likely contributes to adverse health outcomes [5]. For example, multi-morbidity has been shown to increase the likelihood of hospital admissions, increase length of stay and the readmission rate. It has also been shown to negatively

impact on healthcare costs, reduce quality of life and increase the prevalence of dependency, polypharmacy and mortality [6].

With increasing ageing of the population, it is projected that from the years 2015 to 2035, the number of people living with ≥4 comorbidities will almost double (from 9.8% to 17.0%) and more than two thirds of gains in life expectancy after the age of 65 years will be spent living with ≥4 long-term conditions [7]. Comorbidity associated with increased age will lead to the emergence of complex health states that tend to occur later in life and are commonly called geriatric syndromes that include frailty.

## 4. Frailty

Frailty is defined as a state of increased vulnerability to physical or psychological stressors because of decreased physiological reserve in multiple organ systems that cause limited capacity to maintain homeostasis [8]. The prevalence of frailty in older people > 65 years reaches up to 7% and up to 40% in those >80 years [9]. In a systematic review of observational population-based studies, the prevalence of frailty was 14%-24%. This increased with age and was associated with a poor survival in a dose-response manner [10].

The incidence of frailty is also high. In a systematic review of 46 observational studies involving 120,805 non-frail (robust or pre-frail) community-dwelling participants who were ≥60 years old, from 28 countries, and who survived the median follow up period of 3 years, 13.6% became frail (incidence rate 43.4, 95% confidence interval {CI} 37.3 to 50.4, cases per 1000 person-years). The incidence of frailty was significantly higher in pre-frail individuals than robust individuals (incidence rates, 62.7%, 95% CI 49.2 to 79.8 and 12.0%, 95% CI 8.2 to 17.5, cases per 1000 person-years, respectively, P <0.001). Among robust individuals in 21 studies who survived a median follow-up of 2.5 years, 30.9% became pre-frail, with the pooled incidence rate 150.6 (95% CI 123.3 to 184.1) cases per 1000 person-years. Results of this study suggest that community-dwelling older people are prone to developing frailty [11].

## 5. COVID-19

The respiratory disease COVID-19 is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The SARS-CoV-2 is a zoonotic virus similar to the previous corona viruses that caused the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS). All the three viral infections commonly present with respiratory symptoms and lead to adverse clinical outcomes especially related to ageing, underlying comorbidities and frailty.

### *5.1 Ageing-Related Risk*

In an epidemiological report of 72,314 cases of COVID-19 in China, the majority of cases (89.8%) were between the age of 30 to 79 years old and the proportion of cases in the elderly (> 60 years) was 44.1%. The overall case mortality rate (CFR) was 2.3%, which increased proportionally with age. The CFR in those aged 70 to 79 years was 8.0% and in those aged ≥80 years was 14.8% [12]. ~~In~~ A study of 48,557 cases and 2,169 deaths, conducted in Wuhan China estimated that the risk of

mortality from the time of onset of symptoms in those aged >59 years was 5.1 (95% CI 4.2 to 6.1) times greater than those aged 30-59 years [13].

Older age was identified as a risk factor for mortality from COVID-19 pneumonia in a Chinese retrospective, multicentre cohort study ({odds ratio (OR) 1.10, 95% confidence interval (CI) 1.03 to1.17, p=0·004) [14]. Ageing has also been found to predict severity of disease. In a Chinese clinical progression study of COVID-19, age (OR 1.06) was independently associated with ICU admission in multivariate logistical analysis [15].

In another study, old age was a significant risk factor for the development of acute respiratory distress syndrome (ARDS) and the progression from ARDS to death ({hazard ratio (HR) 3.26, 95% CI 2.08 to 5.11; and 6.17, 3.26 to 11.67, respectively) [16]. Ageing appears to play a significant role in mortality rate differences between countries affected. For example, the overall case-fatality rate in Italy (7.2%) is substantially higher than that in China (2.3%) but when data are stratified by age groups, the case-fatality rate in Italy and China appear very similar up to the age of 69 years. Individuals aged ≥70 years represent 37.6% of cases in Italy and only 11.9% in China from which we may infer that the higher overall case-fatality rate is due to the high prevalence of older age groups in Italy compared to China [17]. Also, in an initial British report of 16,749 patients with severe COVID-19 who were hospitalised, the median age was 72 years (IQR 57, 82). Increasing age was a strong predictor of in-hospital mortality after adjusting for comorbidity (reference age <50 years, 50-69yrs HR 4.02 (95% CI 2.88 to 5.63, p<0.001), 70-79yrs HR 9.59 (6.89 to 13.34, p<0.001), ≥80yrs HR 13.59 (CI 9.79 to 18.85, p<0.001) [18]. Finally, the recently reported British database analysis of 17,425,445 NHS registered adults showed that 5,683 deaths were attributed to COVID-19 and mortality was strongly and proportionally associated with age. With the data being fully adjusted and the 50-59 age group being used as a reference point, those aged 18-<40 had a risk of only 0.07 (95% CI 0.05 to 0.1), whereas those in the ≥80 years age group had a 12.64-fold (95% CI 11.19 to 14.28) increased risk of death from COVID-19 [19].

### *5.2 Comorbidity-Related Risk*

The Chinese epidemiological report of 72,314 cases of COVID-19 showed that the CFR was high among patients with pre-existing comorbid conditions. CFR was 10.5% for patients with cardiovascular disease, 7.3% for diabetes mellitus, 6.3% for chronic respiratory disease, 6.0% for hypertension and 5.6% for cancer [12]. In a meta-analysis of 7 studies including 1,576 patients with COVID-19, the most prevalent comorbidities were hypertension (21.1%, 95% CI 13.0 to 27.2%), diabetes (9.7%, 7.2 to 12.2%), cardiovascular disease (8.4%, 3.8 to 13.8%) and respiratory disease (1.5%, 0.9 to 2.1%). The pooled odds ratio (OR) for severe illness prediction were 2.36 (95% CI 1.46 to 3.83) for hypertension, 2.46 (1.76 to 3.44) for respiratory disease and 3.42 (1.88 to 6.22) for cardiovascular disease respectively [2].

In another meta-analysis of 6 studies including 1,527 patients with COVID-19, the incidences of hypertension, cardio-cerebrovascular disease and diabetes mellitus were twofold, threefold and fourfold respectively higher in severe intensive care unit (ICU) patients compared to severe non-ICU patients [20]. In a Chinese nationwide analysis of 1,590 hospitalised patients with COVID-19, conducted to evaluate the composite endpoints of admission to intensive care unit, invasive ventilation or death, 8.2% patients reached ~~to~~ the composite endpoints. A minimum of one comorbidity was present in 25.1% of patients. Two or more comorbidities were reported in 8.2%

of patients. The composite endpoint was documented in 28.5% of patients who had two or more comorbidities, 19.3% of patients who had at least one comorbidity as opposed to 4.5% patients without comorbidities. Significantly, more patients with hypertension (19.7% vs. 5.9%), cardiovascular diseases (22.0% vs. 7.7%), cerebrovascular diseases (33.3% vs. 7.8%), diabetes (23.8% vs. 6.8%), COPD (50.0% vs. 7.6%), chronic kidney diseases (28.6% vs. 8.0%) and malignancy (38.9% vs. 7.9%) reached the composite endpoints compared to those without. Risk factors for reaching the composite end points were COPD {hazards ratio (HR) 2.681, 95% CI 1.424 to 5.048}, diabetes (1.59, 1.03 to 2.45), hypertension (1.58, 1.07 to 2.32) and malignancy (3.50, 1.60 to 7.64) after adjusting for age and smoking status. The HR was 1.79 (95% CI 1.16 to 2.77) among patients with at least one comorbidity and 2.59 (95%CI 1.61 to 4.17) among patients with two or more comorbidities. This analysis suggests that number of comorbidities proportionally increases the risk of adverse outcomes [21].

In Italy, a chart review of 355 patients who died with COVID-19 showed the mean (SD) number of comorbidities was 2.7 (1.6). Overall, 0.8% of patients had no comorbidities, 25.1% had one comorbidity, 25.6% had 2 comorbidities and 48.5% had ≥3 comorbidities suggesting that mortality is proportional to number of comorbidities [17]. In the British report of 20,133 patients hospitalised with severe COVID-19, 77% had a documented comorbidity which was associated with increased hospital mortality [18]. Available data from the countries most prominently affected by COVID-19 is summarised in Table 1 [17, 18, 21, 22].

### *5.3 The Frailty Factor*

Frailty is characterised by dysregulation in the innate and adaptive immunity that leads to chronic inflammation and increased susceptibility to severe infections. It may be linked to infectious diseases through common pathways that reduce immunity and increase inflammatory markers. Raised inflammatory markers are a common finding in patients with viral pneumonia [23]. Frailty has also been shown to be associated with poor post-vaccination immune response, increased rates of influenza-like illness and laboratory-confirmed influenza infection [24]. Although frailty was not formally assessed in the published COVID-19 studies, it is possible that it was an important factor that contributed to adverse outcomes. This is not surprising as the official estimates published by the Belgian, French, Irish and Italian governments estimates the proportion of deaths from Covid-19 among care home residents to be 42% to 54% [25]. It is also reported that there have been large numbers of deaths in care homes in Italy, Spain, the United Kingdom and the United States but official data for these countries is either incomplete or difficult to interpret [25].

In a US long-term care facility report of 101 residents with COVID-19, the median age was 83 years (range, 51 to 100), hospitalization rate was 54.5% and case fatality rate was 33.7%. Most (94.1% of 101) facility residents had chronic underlying health conditions, with hypertension (67.3%), cardiac disease (60.4%), renal disease (40.6%), diabetes mellitus (31.7%), pulmonary disease (31.7%), obesity (30.7%) and cancer (14.9%) being most common [26]. The results suggest that frail care home residents affected by COVID-19 are older than those reported from other community settings and also the number of comorbidities is higher. Interestingly, the majority of patients (68.3%) were female in contrast to the higher incidence of COVID-19 in males reported

elsewhere in community settings. This is likely reflecting the predominance of females in care homes due to their longer life expectancy.

**Table 1** International reported data on COVID-19 patients characteristics.

| Country | Population | Main findings |
|---|---|---|
| **China** [21] | 1,590 patients. | A. Mean (SD) age was 48.9 (16.3) years<br>B. 25.1% have≥1 comorbidity<br>C. Prevalent comorbidities were hypertension (16.9%) and diabetes (8.2%)<br>D. Mortality risk increased by comorbidity (HR 1.79, 95% CI 1.16 to 2.77) for ≥1 comorbidity and 2.59 (1.61 to 4.17) for ≥2 comorbidities. |
| **Italy** [17] | 1625 died patients | A. Overall case fatality rate 7.2%, 52.3% were ≥80 years old.<br>B. Analysis of subsample of 355 patients:<br>1. Mean (SD) age 79.5 years (8.1).<br>2. Mean (SD) number of comorbidities 2.7 (1.6).<br>3. 99.2% of patients had ≥1 comorbidity.<br>4. Comorbidities were diabetes mellitus (35.5%), ischaemic heart disease (30%), atrial fibrillation (24.5%), active cancer (20.3%), stroke (9.6%) and dementia (6.8%).<br>5. Presence of comorbidities increased risk of mortality. |
| **UK** [18] | 20,133 patients. | A. Median age 73 years (IQR 58, 82).<br>B. 77% had documented comorbidity.<br>C. Common comorbidities were: cardiac disease (31%), uncomplicated diabetes (21%), non-asthmatic chronic respiratory disease (18%), and CKD (16%).<br>D. Mortality rate 26%.<br>E. Increased age and morbidity predicted mortality. |
| **USA** [22] | 5,700 patients | A. Median age, 63 years (IQR 52-75).<br>B. Common comorbidities were hypertension (56.6%), obesity (41.7%) and diabetes (33.8%).<br>C. Median score on the Charlson Comorbidity Index was 4 points (IQR 2-6).<br>C. Outcomes were assessed for 2,634 patients:<br>1. ICU admission, 373 patients (14.2%).<br>2. Mechanical ventilation, 320 (12.2%).<br>3. Renal replacement therapy, 81 (3.2%).<br>4. Mortality, 553 (21%). |

### *5.4 Synergistic Effect*

Ageing and frailty exert a negative effect on the immune system that leads to an increased risk of infection. The ageing immune system is characterized by a low grade and chronic systemic inflammatory state or “InflammAgeing” marked by elevated inflammatory markers such as IL- 6

and C-reactive protein and is associated with an increased susceptibility to infection [27]. It has been shown that the immune response in patients with COVID-19 is dysregulated and the SARS-CoV-2 might mainly act on lymphocytes, (in particular T lymphocytes), induce a cytokine storm in the body, and generate a series of immune responses to damage the corresponding organs [28]. Therefore, immune dysregulation and prolonged inflammation, both of which are prevalent in frailty, may be the key drivers of poor clinical outcomes in patients with Covid-19. Comorbidity and frailty also often overlap and lead to impairment in functional status, quality of life and worse prognosis [29]. It has been shown that 82% of community dwelling older people who are frail also have comorbidities, 29% have disability in at least one activity of daily living and 93% have disability in at least one instrumental activity of daily living [30]. Therefore, ageing, comorbidity and frailty appear to overlap and exert a synergistic effect in older people that increases their vulnerability to infection and risk of adverse outcomes (Figure 1). Also, frailty appears to predict the outcome of COVID-19 better than either age or comorbidity. In a recent multicentre European cohort study, frailty, assessed by clinical frailty score (CFS), proportionately predicted mortality. Compared with CFS 1–2, the adjusted hazard ratios for time from hospital admission to death were 1.55 (95% CI 1.00 to 2.41) for CFS 3–4, 1.83 (1.15 to 2.91) for CFS 5–6, and 2.39 (1·50 to 3·81) for CFS 7–9, and adjusted odds ratios for day-7 mortality were 1.22 (95% CI 0.63 to 2·38) for CFS 3–4, 1.62 (0.81 to 3.26) for CFS 5–6, and 3.12 (1.56 to 6.24) for CFS 7–9 [31].

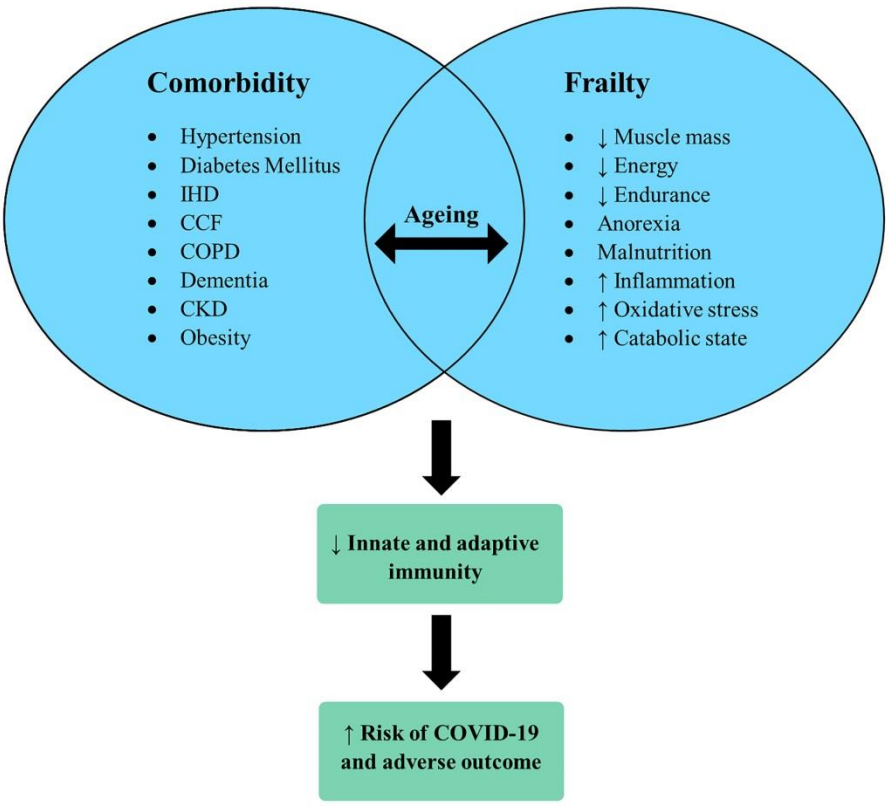


**Figure 1** Synergistic effect of aging, comorbidity and frailty reducing immunity and increasing the risk of COVID-19 infection and adverse outcomes. IHD=Ischaemic heart disease, CCF=Congestive cardiac failure, COPD=Chronic obstructive pulmonary disease, CKD=Chronic kidney disease.

## 6. Conclusions

The global demographics are shifted towards older age. Ageing is associated with increased prevalence of comorbidity and frailty that increase the risk of infections due to dysregulation of the immune system. In addition to the recent COVID-19 pandemic, it has been previously shown that the mortality from influenza was higher in patients who had chronic obstructive pulmonary disease (OR 1.49, 95% CI 1.10 to 2.01), cardiovascular disease (2.92, 1.76 to 4.86) or hypertension (1.49, 1.10 to 2.10) compared to patients with no comorbidities [32]. Ageing, comorbidity and frailty are also associated with chronic inflammation that is shared with the features of infectious diseases [33]. It has also been shown that lymphocyte number and function are reduced in patients who have died from viral pneumonia compared to those who have survived suggesting that the levels of inflammatory factors in the deceased group were higher than those in the survival group [34].

Both ageing and frailty are indicators of immunosuppression and are significantly associated with worse outcomes. Frail older people in long-term care facilities are vulnerable to respiratory disease outbreaks, including influenza and other human coronaviruses such as the common cold [35, 36]. Frailty has also been associated with poor post-vaccination immune response and an increased risk of influenza [37]. Frail nursing home residents admitted to hospital were found to be at an increased risk of viral pneumonia (relative risk {RR} 3.06, $P = 0.01$) compared to those admitted from the community [38]. Therefore, older people with COVID-19 are more likely to have underlying comorbidity and frailty which are detrimental to prognosis. These patients may die because of their underlying comorbid conditions. Thorough and systematic assessment of these patients is required from the outset as COVID-19 affects almost all organ systems. These patients require treatment of their pre-existing conditions in addition to the treatment of COVID-19 to reduce the risk of multi-organ failure. Decisions regarding escalation of treatment should include frailty assessment in addition to overall comorbid condition and function. Therefore, frailty score should be part of the initial assessment of patients [39].

## 7. Future Perspectives

So far, there is no specific antiviral agent for COVID-19. Research is currently on-going to develop effective treatment as well as protective vaccination. Due to impaired immunity in older people with comorbidity and frailty, these factors should be considered in risk assessment models in future clinical trials to ensure that the developed vaccines have a good immunogenic response in frail individuals. It appears that COVID-19 mortality is concentrated in older people. Aged population is currently concentrated in the wealthier developed countries, which are able to absorb the financial impact of the pandemic and limit its spread to other countries.

With the global demographic shift towards old age, the sector of older people will exponentially expand, especially in low and middle income countries where heath care resources to face a future pandemic are limited and thus increases the risk of uncontrollable global spread. Therefore, WHO and governments around the world must consider this potential threat in health care planning. Reducing the frailty and comorbidity burden of the future ageing population will be a global necessity. Also, care home populations will increase and future review of policies and

regulations of these institutions will be required to avoid a future outbreak in these vulnerable settings.

## 8. Key Points

- COVID-19 pandemic is largely concentrated in older people with comorbidity and frailty.
- Age, comorbidity and frailty are synergistic risk factors for COVID-19 adverse outcomes.
- With the demographic shift toward old age, global health care planning is required to improve our resilience for potential future pandemics.

## Author Contributions

Authors contributed equally to the writing of this manuscript.

## Competing Interests

The authors have declared that no competing interests exist.

## References

1. Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020; 91: 264-266.
2. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: A systematic review and meta-analysis. Int J Infect Dis. 2020; 94: 91-95.
3. Ageing and health. World Health Organisation. Accessed May 2020.
4. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med. 2002; 162: 2269-2276.
5. Karlamangla AS, Singer BH, McEwen BS, Rowe JW, Seeman TE. Allostatic load as a predictor of functional decline: MacArthur studies of successful aging. J Clin Epidemiol. 2002; 55: 696-710.
6. Salive ME. Multimorbidity in older adults. Epidemiol Rev. 2013; 35: 75-83.
7. Kingston A, Robinson L, Booth H, Knapp M, Jagger C, MODEM project. Projections of multi-morbidity in the older population in England to 2035: Estimates from the Population Ageing and Care Simulation (PACSim) model. *Age Ageing.* 2018; 47: 374-380.
8. Bergman H, Ferrucci L, Guralnik J, Hogan DB, Hummel S, Karunananthan S, et al. Frailty: An emerging research and clinical paradigm-issues and controversies. J Gerontol A Biol Sci Med Sci. 2009; 62: 731-737.
9. Morley JE. Diabetes, sarcopenia, and frailty. Clin Geriatr Med. 2008; 24: 455-469.
10. Shamliyana T, Talley KMC, Ramakrishnan R, Kane RL. Association of frailty with survival: A systematic literature review. Ageing Res Rev. 2013; 12: 719-736.
11. Ofori-Asenso R, Chin KL, Mazidi M, Zomer E, Ilomaki J, Zullo AR, et al. Global incidence of frailty and prefrailty among community-dwelling older adults a systematic review and meta-analysis. JAMA Netw Open. 2019; 2: e198398.

12. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA.* 2020; 323: 1239-1242.
13. Wu JT, Leung K, Bushman M, Kishore N, Niehus R, de Salazar PM, et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. Nat Med. 2020; 26: 506-510.
14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020; 395: 1054-1062.
15. Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect. 2020; 80: e1-e6.
16. Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et al. Risk Factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020; 180: 1-11.
17. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA.* 2020. doi:10.1001/jama.2020.4683.
18. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. BMJ 2020; 369: m1985.
19. Williamson E, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. OpenSAFELY: Factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. MedRxiv. doi: https://doi.org/10.1101/2020.05.06.20092999.
20. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020; 109: 531-538.
21. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. Eur Respir J. 2020; 55: 2000547.
22. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA.* 2020; 323: 2052-2059.
23. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, et al. Clinical features predicting mortality risk in patients with viral pneumonia: The MuLBSTA Score. Front Microbiol. 2019; 10: 2752.
24. Yao X, Hamilton RG, Weng NP, Xue QL, Bream JH, Li H, et al. Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults. Vaccine. 2011; 29: 5015-5021.
25. Mortality associated with COVID-19 outbreaks in care homes: Early international evidence. LTC responses to COVID-19. International Long-Term Care Policy Network. Accessed on 14th may 2020.
26. McMichael TM, Currie DW, Clark S, Pogosjans S, Kay M, Schwartz NG, et al. Epidemiology of Covid-19 in a long-term care facility in King County, Washington. NEJM. 2020; 382: 2005-2011.
27. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000; 908: 244-254.

28. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis. 2020;* ciaa248. doi: 10.1093/cid/ciaa248.
29. Henchoz Y, Büla C, Guessous I, Santos-Eggimann B. Association between physical frailty and quality of life in a representative sample of community-dwelling swiss older people. J Nutr Health Aging. 2017; 21: 585-592.
30. Wong CH, Weiss D, Sourial N, Karunananthan S, Quail JM, Wolfson C, et al. Frailty and its association with disability and comorbidity in a community-dwelling sample of seniors in Montreal: A cross-sectional study. Aging Clin Exp Res. 2010; 22: 54-62.
31. Hewitt J, Carter B, Vilches-Moraga A, Quinn TJ, Braude P, Verduri A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): A multicentre, European, observational cohort study. Lancet. 2020; S2468-2667(20)30146-8. doi: 10.1016/S2468-2667(20)30146-8.
32. Mertz D, Kim TH, Johnstone J, Lam PP, Kuster SP, Fadel SA, et al. Populations at risk for severe or complicated influenza illness: Systematic review and meta-analysis. BMJ. 2013; 347: f5061.
33. Odegaard JI, Chawla A. Connecting type 1 and type 2 diabetes through innate immunity. Cold Spring Harbor Perspect Med. 2012; 2: a007724.
34. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, et al. Clinical features predicting mortality risk in patients with viral pneumonia: The MuLBSTA Score. Front Microbiol. 2019; 10: 2752.
35. Lansbury LE, Brown CS, Nguyen-Van-Tam JS. Influenza in long-term care facilities. Influenza Other Respir Viruses. 2017; 11: 356-366.
36. Hand J, Rose EB, Salinas A, Lu X, Sakthivel SK, Schneider E, et al. Severe respiratory illness outbreak associated with human coronavirus NL63 in a long-term care facility. Emerg Infect Dis. 2018; 24: 1964-1966.
37. Yao X, Hamilton RG, Weng NP, Xue QL, Bream JH, Li H, et al. Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults. Vaccine. 2011; 29: 5015-5021.
38. Ma HM, Lee KP, Woo J. Predictors of viral pneumonia: The need for viral testing in all patients hospitalized for nursing home-acquired pneumonia. Geriatr Gerontol Int. 2013; 13: 949-957.
39. COVID-19 Rapid Guideline: Critical Care in Adults; NICE Guideline [NG159]. 2020. Available online: https://www.nice.org.uk/guidance/ng159/chapter/1-Admission-to-hospital (accessed 15th May 2020).


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# Bone Mineral Density in Male Hospital Physicians over the Age of 65 Years

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**Abstract**

Hospitalists are at risk for vitamin D deficiency during their active years due to indoor working conditions and insufficient sunlight exposure. The impairment of bone mineral density (BMD) in this group has not been studied. A total of 50 male hospitalists aged ≥ 65 years were enrolled. Their BMD was measured at the femoral neck (FN), lumbar spine (LS), and distal radius (DR), and their medical history and risk factors were assessed through a detailed questionnaire. The FRAX® (Fracture risk assessment tool) score was calculated for each participant. The mean age was 71 ±5.3 years. They worked as hospital physicians for a mean duration of 38.8 ±6.9 years. According to the BMD measurement, 15 (30%) had osteoporosis, and 29 (58%) had osteopenia. We also analyzed bone density excluding DR, since the clinical significance of low bone density of DR alone is debatable. In this analysis, 7 doctors (14%) had osteoporosis, and 33 (66%) had osteopenia. According to AACE/ACE 2016 guidelines, 48% of the participants would require specific treatment for fracture prevention.

However, using only FN and LS BMD, 40% would require treatment. Hospitalists were found to have a high prevalence of osteoporosis and osteopenia, and 40% required specific treatment according to international guidelines.

**Keywords**
Osteoporosis; osteopenia; bone mineral density; male physician; hospitalist

## 1. Introduction

Severe vitamin D deficiency in childhood is known to cause rickets; however, this is rare in the developed world, in contrast to mild to moderate vitamin D deficiency that frequently occurs across all age groups [1]. Vitamin D deficiency contributes to the development of osteoporosis and osteomalacia and is associated with an increased risk of bone fractures in the elderly, bone-related pain, diabetes mellitus [2], cardiovascular disease [3], and an increase in cancer mortality [4], whereas vitamin D supplementation is associated with decreased total mortality rate [5].

Solar ultraviolet-B irradiation is the primary source of vitamin D for most people, while dietary sources are limited. Therefore, sunlight exposure is an important factor in serum 25(OH)D levels. Exposure varies seasonally, and certain populations are not exposed to sunlight due to limited mobility or traditional dress. In recent years, many large observational studies have found evidence of vitamin D deficiency, even in young and healthy subjects. Vitamin D inadequacy was reported in approximately 36% of otherwise healthy adults, in up to 57% of general medicine inpatients in the United States and even higher in Europe [1]. Even in sunny countries such as Israel, hypovitaminosis D is prevalent. In a study published in 2009, four consecutive measurements of vitamin D, were taken in outdoor and indoor Israeli workers, once per season. Among this working population, optimal vitamin D status (≥75 nmol/L) was achieved only in summer by males working either outdoors or indoors [6].

Hospitalists are at-risk for vitamin D deficiency due to long hours of indoor work with little sun exposure [7, 8].

In a previous study performed in our institution [9], vitamin D levels of 51 young hospitalists were compared to those of young community-based physicians, at the end of winter, and the mean serum level of 25(OH)D among the hospital physicians was found to be significantly lower than that of community-based physicians.

In a recent systematic review on vitamin D levels in different occupations [10], the overall mean serum 25(OH)D levels of all healthcare workers were 61.6 ±11.0 nmol/L (data from 19,083 study subjects from 35 studies). Among healthcare workers, medical residents and healthcare students had the lowest levels of circulating vitamin D (44.0 ±8.3 nmol/L and 45.2 ±5.5 nmol/L, respectively). Up to 95% of healthcare workers had vitamin D insufficiency.

In our study, we examined hospital physicians and pensioners, a group at risk for low vitamin D levels in their younger years, to explore the possible effects of this deficiency on bone density after several years. Osteoporosis is more common in women than in men and has therefore been studied more extensively in women. However, osteoporosis in men is an important public health problem with associated morbidity and mortality at a significant level [11].

## 2. Materials and Methods

The study was conducted in the Shaare Zedek Medical Center (SZMC), a 1000-bed teaching hospital in Jerusalem. The study group consisted of male hospital physicians aged 65 and older, who were invited to participate through email and telephone.

We excluded doctors who did not consistently work in a hospital during their careers, were currently receiving chronic steroid treatment, had malabsorption, chronic kidney disease with GFR<60, osteoarthritis, a current cancer diagnosis that involved endocrinological abnormalities or treatment that could affect bone density (including androgen-deprivation therapy), and doctors with known osteoporosis [12].

Osteopenia and osteoporosis were defined according to the World Health Organization (WHO) criteria [13].

### *2.1 Protocol*

Each participant filled in a questionnaire detailing age, the field of medical specialty, number of years having worked as a hospital doctor, and status as a Holocaust survivor, as well as his medical history regarding the exclusion criteria and FRAX® (Fracture risk assessment tool) variables.

For Bone Mineral Density (BMD) measurement, all participants were tested using the dual-energy x-ray absorptiometry (DXA) device–a Hologic QDR Series X-Ray Bone Densitometer. The BMD was measured at the femoral neck (FN), lumbar spine (LS), and distal radius (DR). All subjects were tested by the same experienced technician, and the lumbar vertebrae were marked manually.

FRAX® score was calculated for each participant using FRAX® ISRAEL data at the Sheffield University website [14]. It is a fracture risk assessment tool that has been developed by Sheffield University and estimates the 10-year probability of hip fracture and major osteoporotic fracture, in order to help health care professionals identify patients who need pharmacologic treatment. It is based on data collected from large observational studies and global population. The FRAX® score calculation includes age, gender, weight, height, clinical risk factors (previous fracture, parent hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and alcohol use), and femoral neck BMD ($g/cm^2$). The FRAX® score prediction accuracy has been validated in many independent studies [15].

The institutional review board of Shaare Zedek Medical Center provided approval for this study. Each participant signed an informed consent form.

### *2.2 Statistical Methods*

Demographic and clinical characteristics were analyzed descriptively as numbers and percentages or means and standard deviations, as appropriate.

To test the association between two categorical variables, the Chi-square test was applied. Pearson's correlation coefficient was calculated to assess the correlation between two quantitative variables. A P-value of 5% or less was considered statistically significant.

The SPSS 21.0 statistical software package (SPSS Inc., Chicago, IL, U.S.A.) was used to perform the statistical analysis.

## 3. Results

Out of the 110 physicians invited to participate in the study, 8 (7%) were excluded according to the exclusion criteria, and 52 (46%) declined to participate. A total of 50 physicians were included in the final statistical analysis. Their characteristics are shown in Table 1. The mean age was 71 ±5.3 years, and they worked as hospital physicians for 38.8 ±6.9 years. There were 15 (30%) who had osteoporosis at one of the sites measured, 29 (58%) had osteopenia, and 6 (12%) had normal bone density (Figure 1). We also analyzed bone density excluding DR, since the clinical significance of low bone density of DR alone is debatable (Figure 1). In this analysis, 7 doctors (14%) had osteoporosis, 33 (66%) had osteopenia, and 10 (20%) had normal bone density.

**Table 1** Participants' characteristics (N = 50).

| | |
|---|---|
| **Age** (years, mean ±SD) | 71 ±5.3 |
| **Years as a hospital physician** (years, mean ±SD) | 38.8 ±6.9 |
| **BMI** (mean) | 26.3 |
| **Medical History** | |
| Renal Failure | 1 (2%) |
| Cancer (past) | 3 (6%) |
| Smoker | 2 (4%) |
| Holocaust survival | 5 (10%) |
| Steroid treatment (present or past) | 1 (2%) |
| Hyperthyroidism | 2 (4%) |
| S/P Gastrectomy | 2 (4%) |

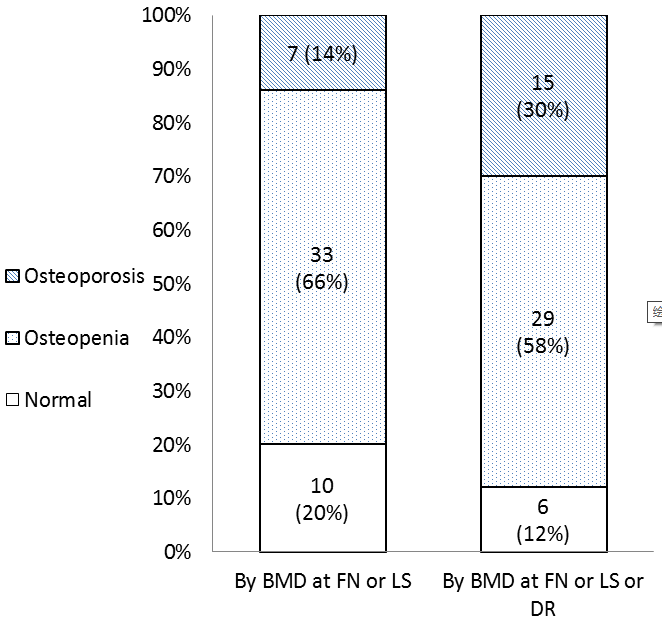


**Figure 1** Diagnosis by BMD. BMD: Bone Mineral Density; FN: Femoral Neck; LS: Lumbar Spine; DR: Distal Radius.

The FRAX® score was calculated for each participant, and we used AACE/ACE 2016 guidelines to define the participants who required specific therapy for fracture prevention, i.e., a participant who had osteoporosis at one of the sites or osteopenia with a high FRAX® score (Figure 2). This analysis showed that 48% of the participants would require specific pharmacologic treatment for fracture prevention. However, 40% would require treatment, using only FN and LS BMD.

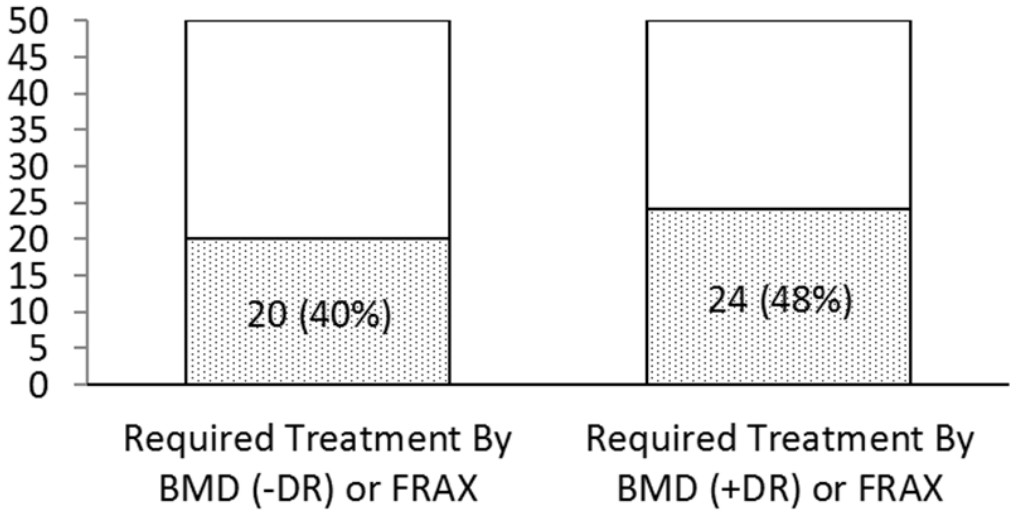


**Figure 2** Required metabolic treatment by BMD result and/or FRAX score. BMD (–DR): Bone Mineral Density at Femoral Neck or Lumbar Spine; BMD (+DR): Bone Mineral Density at Femoral Neck or Lumbar Spine or Distal Radius.

## 4. Discussion

The prevalence of osteoporosis or osteopenia in hospital physicians over the age of 65, was found to be 30% and 58%, respectively. It might be explained, partly by vitamin D deficiency, which was observed in a similar population in a previous study. Another factor that can influence BMD in this population is the low level of physical activity due to heavy workload.

The use of BMD as a screening test for men is debatable. Certain expert groups recommend screening for men aged 70 years and older [16, 17], or 65 and older [18], while others do not recommend screening [19, 20]. Although about 30% of the hip [21] and 33% of vertebral fractures occur in males [22], most men do not undergo BMD testing, and considerably less epidemiological data are available for men than women.

There is no data on the presence of osteopenia and osteoporosis in the Israeli male population to directly compare the study results. The data on the prevalence of osteopenia or osteoporosis in men worldwide are limited. Most of the data are derived from the National Health and Nutritional Examination Survey (NHANES), which is published periodically and from the MrOS study. The NHANES survey in the US in 2005–2010 found osteoporosis in 5% of men at the ages 70–79 and osteopenia in 41.8%, using FN and LS BMD [23]. In our study, the prevalence of osteoporosis was 5% and of osteopenia 85% in the age group of 70–79 years (using FN and LS BMD). The prevalence of osteopenia in our study was higher than the earlier reported prevalence, while the mean age in our study was 71 and only 5 doctors were 80 years and older. The MrOS study [24] found osteoporosis in 3.3% of men older than 65 years, which was lower than in our study. The low bone

mass was defined as T score lower than –1.5, which was not in accordance with the WHO definition. These definitions were different than those used in our study, thus precluding comparison regarding the prevalence of osteopenia. Another study from Japan [25], on 144 men over 65 years who visited a dental clinic, found osteoporosis in 47 (33%) and osteopenia in 42 (29%) men, but the BMD test was different from the current study. It was measured at the calcaneus by ultrasound densitometry, thus, making the comparison to the results in our study inarticulate.

There is controversy regarding distal radius BMD. It can predict fractures in men [26, 27] and is rarely affected by osteoarthritis, as opposed to the spine and hip. Therefore, it may be a sensitive test for osteoporosis in men. Osteoporosis of DR alone was found in 15% of men aged 70 and older [28]. The Endocrine Society guidelines for osteoporosis in men suggested measuring DR DXA when the spine or hip BMD could not be interpreted, and for men with hyperparathyroidism or on anti-androgen therapy, but it was not recommended routinely [29]. The reason is that there is no scientific evidence showing that men with osteoporosis in the radius exclusively, respond to osteoporosis treatment. According to these guidelines, pharmacologic treatment is recommended for those had fragility fractures of the hip or vertebrae, a T score less than –2.5 in the spine, femoral neck, total hip, or a T score between –1 and –2.5 and a FRAX® ten year probability for any fracture ≥ 20% or 10-year risk of the hip fracture ≥ 3%. The AACE/ACE guidelines for the diagnosis and treatment of postmenopausal osteoporosis of 2016 [30] recommended pharmacologic treatment of patients with similar indications but included DR BMD. In the future, with more data, DR could be included in the guidelines for men. We analyzed our results with and without the DR BMD.

Osteopenia was found in over 60% of our study participants, and more than 10% diagnosed with osteoporosis. This is alarming as due to the lack of routine screening in the male population, many elderly physicians with osteopenia or osteoporosis would not be diagnosed and treated to prevent osteoporotic fractures.

There is a relative lack of epidemiological data and guidelines for osteoporosis screening in men as compared to women. The lifetime risk of osteoporotic fractures in men is estimated to be between 10% and 25%, depending on the population studied, with men experiencing it around ten years later than women. As life expectancy is increasing for men more than women, the prevalence of osteoporotic fractures in men is expected to increase, making them an interesting group to study.

The prevalence of osteoporosis in Holocaust survivors is known to be significantly higher than that of the general population, due to nutritional deficits and lack of exercise and sunlight [31, 32]. There were five of the study participants who were Holocaust survivors. However, it is not possible to conclude the general population of Holocaust survivors because of the small number of Holocaust survivors in the study.

Our study has several limitations. First, the assumption was made, based on previous studies, that young hospital-based doctors have a deficiency of vitamin D when compared to community-based doctors [9], and suboptimal vitamin D levels generally [7, 8]. It is not known whether the specific doctors participating in this study had low vitamin D levels throughout their careers. It was decided not to measure current vitamin D levels at the time of the study, as they may be different from the earlier levels. Also, hypogonadism was one of the questions that were asked to calculate the FRAX® score, but the serum testosterone level was not examined in our study.

Another limitation of this study is the specific study population. It consisted of physicians, and some factors that affect the risk of osteoporosis viz., non-smoking, exercise, and diet, including calcium in this specific population may counteract the effects of lack of vitamin D.

The third limitation is selection bias. The study had an approximately 50% response-rate; as the healthier and more mobile subjects were included due to self-selection. This selection, however, presumptively enhanced the relevance of our results.

## 5. Conclusions

In our trial, we examined BMD in male hospitalists over the age of 65. It seems that hospitalists have a high prevalence of osteoporosis and osteopenia. The data from this study may be useful for the decision of screening tests in this population, as well as designing larger confirmatory studies on the prevalence of osteopenia and osteoporosis in at-risk populations.

## Author Contributions

NS collected part of the data and wrote the main manuscript of the article. CFS collected part of the data and summarized the data, MF analysed the data and wrote part of the main manuscript, GM proposed the initial idea of the trial, made critical revisions, and read and approved the final manuscript.

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## Competing Interests

The authors have declared that no competing interests exist.

## References

1. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clinic Proc. 2006; 81: 353-373.
2. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers and cardiovascular disease. Am J Clin Nutr. 2004; 80: 1678S-1688S.
3. Melamed ML, Muntner P, Michos ED. Serum 25-Hydroxyvitamin D levels and the prevalence of peripheral arterial disease – results from NHANES 2001-2004. Arterioscler Thromb Vasc Biol. 2008; 28: 1179-1185.
4. Keun N, Giovannucci E. Vitamin D supplements and cancer incidence and mortality: A meta-analysis. Br J Cancer. 2014; 111: 976-980.
5. Autier P, Gandini S. Vitamin D supplementation and total mortality, a meta-analysis of randomized controlled trials. Arch Intern Med. 2007; 167: 1730-1737.
6. Azizi E, Pavlotsky F, Vered I. Occupational exposure to solar UVB and seasonal monitoring of serum levels of 25-hydroxy vitamin D3: A case-control study. Photochem Photobiol. 2009; 85: 1240-1244.

7. Haney EM, Stadler D, Bliziotes MM. Vitamin D insufficiency in internal medicine residents. Calcif Tissue Int. 2005; 76: 11-16.
8. Manickam B, Washington T, Villagrana N. Determinants of circulating 25-hydroxyvitamin D and bone mineral density in young physicians. Endocr Pract. 2012; 18: 219-226.
9. Munter G, Levi-Vineberg T, Sylvetsky N. Vitamin D deficiency among physicians: A comparison between hospitalists and community-based physicians. Osteoporos Int. 2015; 26:1673-1676.
10. Sowah D, Fan X, Dennett L, Hagtvedt R, Straube S. Vitamin D levels and deficiency with different occupations: A systematic review. BMC Public Health. 2017; 17: 519.
11. Watts NB. Osteoporosis in Men. Endocr Pract. 2013; 19: 834-838.
12. Berntsen GKR, Fønnebø V , Tollan A. Forearm bone mineral density by age in 7,620 men and women the tromsø study, a population-based study. Am J Epidemiol. 2001; 153: 465-473.
13. Kanis JA, on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007.
14. FRAX® assessment at: https://www.sheffield.ac.uk/FRAX/tool.aspx?country=61.
15. Beaudoin C, Moore L, Gagné M, Bessette L, Ste-Marie LG, Brown JP, et al. Performance of predictive tools to identify individuals at risk of non-traumatic fracture: A systematic review, meta-analysis, and meta-regression. Osteoporos Int. 2019; 30: 721-740.
16. National Ostoporosis Foundation. 2013 Clinician's Guide to Prevention and Treatment of Osteoporosis. http://nof/public/content/resource/913/files/580.pdf.
17. International Society for Clinical Densitometry. 2013 ISCD Official Positions - Adult. At: www.iscd.org/official-positions/2013-iscd-official-positions-adult.
18. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: Summary. CMAJ. 2010; 182: 1864
19. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis. At: www.aace.com/pub/pdf/guidelines/OsteoGuidelines2010.pdf.
20. U.S. Preventive Services Task Force. Screening for Osteoporosis Recommendation Statement. At: www.uspreventiveservicestaskforce.org/uspstf10/osteoporosis/osteors.htm.
21. Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: A world-wide projection. Osteoporos Int. 1992; 2: 285-289.
22. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ 3rd. Incidence of clinically diagnosed vertebral fractures: A population based study in Rochester Minnesota, 1985–1989. J Bone Miner Res. 1992; 7: 221-227.
23. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res. 2014; 29: 2520-2526.
24. Gourlay ML, Overman RA, Fine JP, Filteau G, Cawthon PM, Schousboe JT, et al. Osteoporotic fractures in men (MrOS) research group: Time to osteoporosis and major fracture in older men: The MrOS study. Am J Prev Med. 2016; 50: 727-736.
25. Ohtsuki H, Kawakami M, Kawakami T, Takahashi K, Kirita T, Komasa Y. Risk of osteoporosis in elderly individuals attending a dental clinic. Int Dent J. 2017; 67: 117-122.

26. Gärdsell P, Johnell O, Nilsson BE. The predictive value of forearm bone mineral content measurements in men. Bone. 1990; 11: 229-232.
27. Melton LJ 3rd, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL. Bone density and fracture risk in men. J Bone Miner Res. 1998; 13: 1915-1923.
28. Wiemann LM, Vallarta-Ast N , Krueger D, Binkley N. Effect of female database use for T-score derivation in men. J Clin Densitom. 2007; 10: 244-248.
29. Watts NB, Adler RA, Bilezikian JP, Drake MT, Eastell R, Orwoll ES, et al. Osteoporosis in men: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012; 97: 1802-1822.
30. Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis. Endocr Pract. 2016; 22: 1111-1118.
31. Marcus EL, Menczel J. Higher prevalence of osteoporosis among female Holocaust survivors. Osteoporos Int. 2007; 18: 1501-1506.
32. Kueper J, Beyth S, Liebergall M, Kaplan L, Schroeder JE. Evidence for the adverse effect of starvation on bone quality: A review of the literature. Int J Endocrinol. 2015; 2015: 628740.

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Original Research

# The Effect of Live Bedside Music on Pain in Elderly Surgical Patients. A Unique Collaboration

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**Abstract**

Postoperative pain has a negative influence on physical and mental recovery and may result in a variety of postoperative complications. Listening to recorded music has been revealed to reduce pain, but in addition to that, live bedside music further offers the possibility to interact with the patient, respond to their emotions, and help them in adapting their conditions. It, therefore, seems appropriate for older surgical patients. This study examines the effect of live bedside music on postoperative elderly patients. The study was designed as a prospective clinical pilot study with a control group. During six separate weeks, between September 2016 and May 2017, data were collected using convenience sampling among the postoperative patients aged ≥60 years ($n$ = 35) accounting to 83 sessions. The intervention was live music, person-centred improvisation and existing repertoire, performed by professional musicians of a collaborating conservatoire for 10–15 min, one session a day on three surgical wards of a university hospital. The control group ($n$ = 43; 80 sessions) did not receive the intervention. –The primary endpoint was pain, measured with a visual analog scale (VAS; score 0-10) before the intervention and after 30 minutes and 3 hours of the session. Secondary endpoints were hemodynamic parameters, oxygen saturation, and respiratory rate and anxiety. The Wilcoxon signed-rank test and Mann-Whitney U test were

performed to determine differences within and between groups. Perceived pain was decreased in the live bedside music group at the time of the first post-test and continued to be so for up to three hours ($p$ = .004; $p$ = .000). This decrease in pain was not observed in the control group. There was no clinically relevant effect on secondary endpoints. Live bedside music, performed by professional musicians, has a positive effect on the perceived pain of elderly patients after surgery. Further research on the underlying mechanisms as well as possible clinical implications is required.

**Keywords**
Elderly; live bedside music; surgery; pain; hospital ward

## 1. Introduction

In modern medicine, despite the introduction of new standards and guidelines, up to 40% of patients experience moderate or severe pain after surgery [1]. Inadequate pain management adversely influences physical and psychological factors, which may lead to severe complications, such as delirium, pneumonia, anxiety, stress, and delayed wound healing [2, 3]. Elderly patients experiencing pain can be given less pain medications compared with younger patients. Moreover, the elderly are more likely to experience medication-related side effects [4-6]. This is relevant considering that the current prevalence of polypharmacy in the elderly is 40 to 60% [7]. It is pertinent to explore the effect of non-pharmaceutical interventions, which can be provided to a group of potentially vulnerable elderly surgical patients. Some recently conducted studies indicated that recorded music is effective in reducing postoperative pain in elderly patients [8-17]. Music has, to the best of our knowledge, no toxic side effects and therefore seems an attractive intervention for elderly patients who are more prone to develop complications due to their changed physiology and increased vulnerability [18]. Compared to recorded music, live bedside music has the advantage of the possibility to interact with the patient, respond to emotions and adapt to the patient's situation. However, the effect of live bedside music on elderly patients is unknown; therefore, this prospective clinical pilot study with a control group was carried out to investigate the effect of live bedside music on pain in elderly patients after surgery.

## 2. Materials and Methods

The present pilot study was conducted as a part of the Meaningful Music in Health Care project (MiMiC) between September 2016 and May 2017 at the University Medical Center Groningen, the Netherlands, in collaboration with the Prince Claus Conservatoire of Groningen, Netherlands. As per the knowledge of the authors, University Medical Center Groningen is probably the first hospital to collaborate with a conservatoire and combine these two worlds for the benefit of patients. Alteration in the pain perception was the primary endpoint of the present study and measured using a visual analog scale (VAS) after the live bedside music session. Secondary outcomes that were taken into consideration were hemodynamic parameters, oxygen saturation (SpO2), respiratory rate, and anxiety.

### *2.1 Participants and Setting*

Patients admitted to one of the three surgical wards University Medical Center Groningen, the Netherlands took part in the study. No sample size was formally calculated since convenience sampling was done, maintaining the design of the intervention and availability of the musicians. The inclusion criteria were patients were aged 60 years or older and had undergone surgery during this hospital admission. The exclusion criteria were patients with total deafness (perception deafness), the inability to communicate or the unwillingness or inability to provide written informed consent and those.

### *2.2 Music Intervention Procedure*

The pilot study was carried out in six separate weeks, where live bedside music was performed by one to three professional musicians consisting of a clarinettist, flutist, violinist, contrabassist, and cellist (for changing composition). These performing musicians with comprehensive experience were all associated with the conservatoire.

The intervention was planned according to a fixed structure where it was performed once daily in the morning between 11.00 a.m. to 12.15 p.m. The intervention was carried out for six or seven consecutive days, one ward at a time following the fixed structure. Each ward was allowed to participate for two separate weeks, and each day started with a joint session comprising of the musicians, a mediator, the coordinating nurse of the ward, and the researchers. During this session, patients who were present and able to participate were discussed, and the response of the previous day was evaluated. The mediator was responsible for the time schedule and served as an intermediary between the musicians, patients, and healthcare professionals. After the joint session, one of the musicians walked the hallway and played an improvisation to notify the patients that the musicians were present. The patients were visited at their bedside after the walk-around. The music consisted of genre-based improvisation, idiomatic improvisation, the repertoire of the musicians and person-centred improvisation. For person-centred improvisation, the musician asked for input from the patient in the form of a landscape, feeling or colour. Using improvisation, musicians created meaningful communication with the patient and involved the patient in the process of composing music. The music sessions took place in single, double, and quadruple rooms. The doors of individual rooms were closed and the sound for other patients outside the room was blocked. Each session lasted approximately 10 to 15 minutes. One or two pieces were played, depending on the patient's wishes or condition. The musicians performed for approximately 75 min each day, and afterward, there was a brief evaluation in which the experiences were discussed. The participation of patients was allowed until the availability of the musicians in the ward.

### *2.3 Data Collection*

Patients were informed on the day of admission, prior to surgery or as soon as possible, by two trained research assistants. Data on the patient characteristics (age, gender, nationality) and clinical condition were obtained from the patients, which included the date and surgical category, comorbidity using the Charlson Comorbidity Index (CCI), and the patients were further classified according to the American Society of Anesthesiologists (ASA). The degree of pain was measured 30

to 60 min before each intervention (pre-test), and 30 min after the live bedside music session (post-test) and again after three hours (follow-up test).

To correct for natural changes in pain sensation over time, a control group was formed. The same research assistants collected data in the control group in which no live music was played. The data in the control group were collected during six separate weeks for five consecutive days when the musicians were absent. The same inclusion and exclusion criteria and sampling method were used in the control group.

### *2.4 Instruments*

Pain was defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage' [19] and measured using the VAS [20]. The VAS is also employed to measure various subjective clinical phenomena. The patient verbally rates his/her pain on a 10-cm horizontal line. The starting point (0 cm) represents no pain, while the other end (10 cm) represents the unendurable pain. VAS scores are directly proportional to the degree of pain. Hemodynamic parameters and oxygen saturation were kept as secondary outcomes and were measured using a non-invasive bedside monitor (Philips SureSigns VS2). The respiratory rate was computed for one minute. The VAS was also used to measure the degree of anxiety, and it is also directly proportional to the scores [14].

### *2.5 Statistical Analysis*

Statistical analyses are presented using the median (range) and number (%). Data were checked for normal distribution using Q-Q plots and the Shapiro-Wilk test. The independent samples t-test was used to examine the differences in numerical data between the control and live bedside music groups. The chi-squared test was used for the categorical data. Further, if data were normally distributed, the paired samples t-test was used for the within-group analyses; if not, the Wilcoxon signed-rank test was used. To analyze the difference between the groups, the Mann-Whitney U test was used.

All statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Corporation, Armonk, NY). The data were considered statistically significant when $P$-values < 0.05 (two-sided).

### *2.6 Ethical Considerations*

The medical ethics board concluded that this study did not fall within the scope of the Dutch law of Medical Research Involving Human Subjects Act and provided dispensation for further assessment. The study was registered on the national Netherlands Trial Register (trial ID: NTR6046). Commonly used ethical principles in clinical trials were followed. All participating patients in the study signed the written informed consent according to local regulations, and the data collection was done following the Declaration of Helsinki. Participation in the test was solely entitled to make individual decisions about the number of days they wanted to participate, and also, they were allowed to withdraw from the study at any time without consequences for their care.

## 3. Results

Characteristics of the patients and the clinical data of both the control group and intervention groups are detailed in Table 1. The live bedside music group consisted of 43 patients, whereas the control group comprised 35 patients. The median age group of the study population was 70 years, and approximately 60% of the participants were male. Over 50% of the patients underwent intracavitary surgery. The median time of the first participation in the intervention group was two days postoperatively (range 1–36) compared to three days in the control group (range 1–15). Most of the patients participated for once or twice in the control group (79.1%) or the intervention group (65.7%). No significant differences were found in patients and their clinical characteristic data between both the groups. Approximately 40% of the patients declined to participate in research or were not able to participate due to their medical conditions.

**Table 1** Patient characteristics and clinical data.

| **Variables** | **Control group (n = 43)** | **Live bedside music group (n = 35)** | ***p*- value** |
|---|---|---|---|
| Age | 70 (60–86) | 70 (60–88) | .786[x] |
| Gender | | | .820[y] |
| Male | 26 (60.5%) | 20 (57.%) | |
| Female | 17 (39.5%) | 15 (42.9%) | |
| CCI | 3 (0–10) | 4 (0–9) | .104[z] |
| Location of surgery | | | .301[y] |
| Intracavitair | 23 (53.5%) | 19 (54.3%) | |
| Extremity | 17 (39.5%) | 10 (28.6%) | |
| Head-neck area | 3 (7%) | 6 (17.1%) | |
| ASA - classification | 2 (1–4) | 2 (1–3) | .245[y] |
| Days POD of first measurement | 3 (1–15) | 2 (1–36) | .530[z] |
| Number of participated/measured session | 2 (1–5) | 2 (1–7) | .502[z] |
| | 20 (46.5%) | 17 (48.6%) | |
| 1 | 14 (32.6%) | 6 (17.1%) | |
| 2 | 5 (11.6%) | 4 (11.4%0 | |
| 3 | 3 (7%) | 2 (5.7%) | |
| 4 | 1 (2.3%) | 5 (11.4%) | |
| 5 | n.a. | - | |
| 6 | n.a. | 2 (5.7%) | |
| 7 | | | |

Presented as median (range) or number (%). A p-value of < 0.05 was considered significant.

x Independent samples T-Test

y Chi-square Test

z Mann Whitney U test

### *3.1 Pain*

The low pain scores measured on the VAS resulted in positively skewed distributed data and median scores of zero for the live bedside music group (see Table 2). For the sake of illustration, we presented the means of the pain scores of both groups instead of medians in Figure 1a. The *p*-values are based on non-parametric testing. Statistical analysis revealed that a significant diminution was noted between the pre-test and post-test score ($Z$ = –2.916; $p$ = .004) in the live bedside music group that continued up to the follow-up test ($Z$ = –4.200; $p$ = .000). The control group revealed a minimal, non-significant ($Z$ = –0.492; $p$ = .623) change in pain scores in the post-test, and the follow-up test scores did not differ significantly ($Z$ = –0.712; $p$ = .476) when compared to the pre-test. No differences were observed in the baseline pain scores between the groups ($p$ = .525). However, it was evident from the analysis that differences were revealed in the post-test ($U$ = 2518.0; $p$ = .014) and follow-up test ($U$ = 2119.5; $p$ = .005), indicating live bedside group perceived less pain at the post-test and follow-up test compared to the control group. Additional analysis of patients, who underwent major surgery (intracavitair) showed a significant decrease of pain scores on post-test ($Z$ = -2.663; $p$ = .008) and follow-up (Z = -3.531; $p$ = .000) in the intervention group. Patients with minor surgery (head-neck area & extremity) also showed a decline in pain scores, which was only significant at the follow-up test ($Z$ = -2.272; $p$ = .023). A comparison between major and minor surgery showed no significant difference.

**Table 2** Comparison of results in- and between the groups per outcome.

| | **Variables** | | **Control group (median-range)** | **n** | **Live bedside Music group (median-range)** | **n** | ***p*-value** |
|---|---|---|---|---|---|---|---|
| **Primary outcome** | **Pain (VAS: 0–10)** | Pre- test | 0,40 (0–8,40) | 80 | 0,00 (0,00–10,00) | 83 | .525 |
| | | Post- test | 0,15 (0–8,00) | 78 | *0,00 (0,00–10,00)* [1] | 81 | .014* |
| | | Follow-up test | 0,00 (0–8,00) | 73 | *0,00 (0,00–04,00)* [1] | 75 | .005* |
| **Secondary outcomes** | **Heart rate (bpm)** | Pre- test | 79,50 (46–133) | 80 | 80,00 (47–126) | 80 | 0,085 |
| | | Post- test | 76,50 (45–131) | 78 | *79,00 (45–113)* [1] | 78 | 0,126 |
| | | Follow-up test | 80,00 (50–131) | 73 | *78,00 (50–111)* [2] | 73 | 0,8 |
| | **Respiratory rate (n per minute)** | Pre- test | 16,00 (12–24) | 80 | 18,00 (12–28) | 80 | 0,03* |
| | | Post- test | 16,00 (12–24) | 77 | 18,00 (11–30) | 77 | 0,027* |
| | | Follow-up test | 16,00 (12–24) | 73 | 18,00 (10–28) | 73 | 0,022* |
| | **Saturation (%)** | Pre- test | 96,00 (78–100) | 78 | 97,00 (92–100) | 78 | 0.010* |
| | | Post- test | 97,00 (81–100) | 77 | 98,00 (87–100) | 77 | 0,051 |
| | | Follow-up test | 97,00 (87–100) | 72 | 98,00 (89–100) | 72 | 0,001* |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Systolic blood pressure (mmHG)** | Pre- test | 132,00 (83–200) | 80 | 124,00 (95–167) | 80 | 0,038* |
| | Post- test | 134,00 (84–192) | 78 | 125,00 (76–182) | 78 | 0,01* |
| | Follow-up test | 136,00 (64–172) | 73 | 122,00 (90–180) | 73 | 0,017* |
| **Diastolic blood pressure (mmHg)** | Pre- test | 69,00 (42–108) | 80 | 62,50 (28–104) | 80 | ,002* |
| | Post- test | 68,00 (39–101) | 78 | 63,00 (36–116) | 78 | ,004* |
| | Follow-up test | *67,00 (42–95)* [2] | 73 | 61,00 (29–97) | 73 | 0,013* |
| **Mean arterial blood pressure (mmHg)** | Pre- test | 84,00 (51–148) | 78 | 76,00 (48–112) | 78 | 0,001* |
| | Post- test | 86,00 (55–136) | 78 | 78,00 (54–119) | 78 | 0,003* |
| | Follow-up test | *84,00 (55–136* [2] | 73 | *74,00 (45–120)*[2] | 73 | 0,003* |
| **Anxiety (VAS: 0–10)** | Pre- test | 0,00 (0,00–10,00) | 78 | 0,00 (0,00–10,00) | 78 | 0,659 |
| | Post- test | *0,00 (0,00–7,00)* [1] | 78 | *0,00 (0,00–2,70)* [1] | 78 | 0,734 |
| | Follow-up test | *0,00 (0,00–8,00)* [2] | 73 | *0,00 (0,00–2,20)* [2] | 73 | 0,895 |

* sign. >*p,005*

1. significance difference within the group between pre-test and post-test measurement
2. significance difference within the group between pre-test and follow-up test measurement

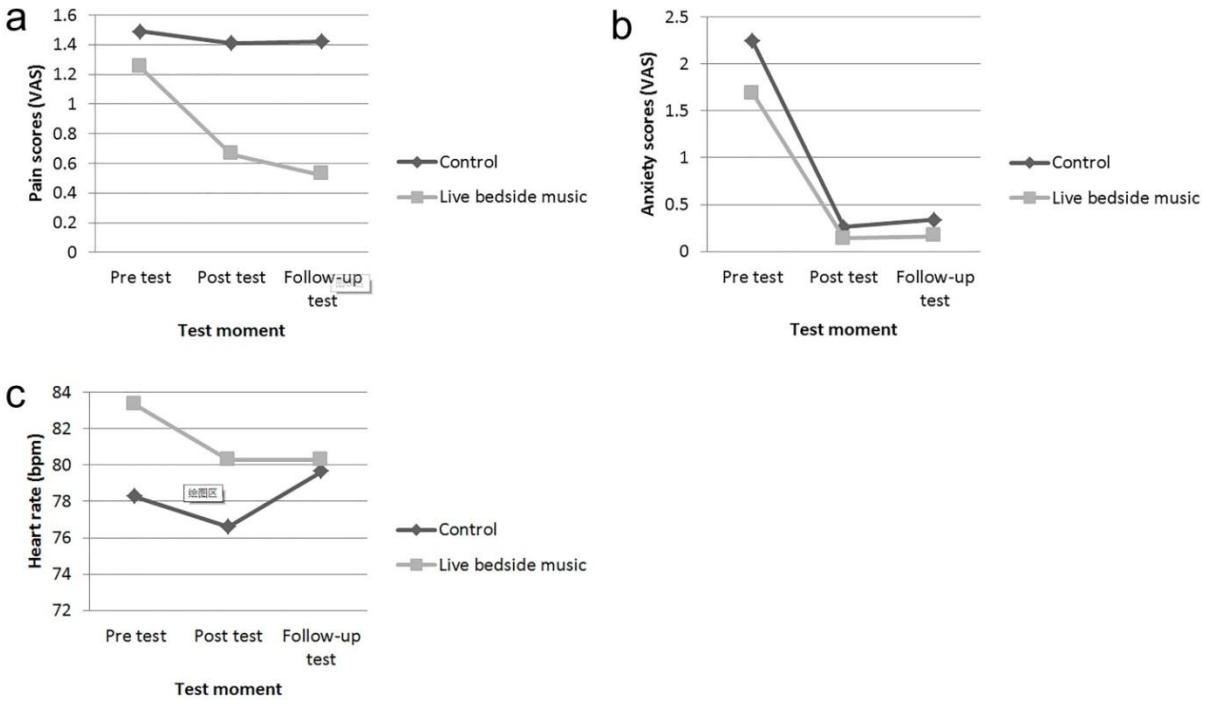


**Figure 1** The dark gray line represents the control group and the light gray line the live bedside music group. a: Mean pain mean scores, measured on a visual analog scale; b: Mean anxiety scores, measured on a visual analog scale; c: Heart rate (bpm, mean values).

### *3.2 Hemodynamic Parameters*

#### 3.2.1 Heart Rate

The results exhibited that the heart rate was significantly reduced in the post-test ($Z$ = –2.759; $p$ = .006) and remained lower at the follow-up test in the live bedside music group ($t$ = 2.757; $df$ = 74; $p$ = .007). Although non-significant, a change was noted in the control group during the post-test measurement. It was observed that the heart rate increased after three hours, exceeding the pre-test (Figure 1b). No significant statistical difference was observed when analyzed by the Mann-Whitney U test between the groups at the three test points.

#### 3.2.2 Blood Pressure

Overall, patients in the control group had higher blood pressure, resulting in a significant difference at pre-test. In both groups, values exhibited a small increase at post-test and a decrease 3 hours later at the follow-up test. In the live bedside music group, these changes were not significant. In the control group, these changes were for the diastolic blood pressure ($t$ = 3.132; $df$ = 72; $p$ = .003) and for the MAP ($Z$ = -2.830; $p$ = .005).

### *3.3 Oxygen Saturation (SpO2) and Respiratory Rate*

There was a significantly higher level of SpO2 at pre-test in the live bedside music group ($Z$ = –2.560; $p$ = .010). In this group, SpO2 rose from a mean level of 97.05 (*SD* 2.33) to 97.35 (*SD* 2.47) at post-test and 97.53 (*SD* 2.35) at follow-up, but not significantly. In the control group, SpO2 rose at post-test from a mean level of 95.47 (*SD* 5.47) to 96.44 (*SD* 3.18), but decreased slightly at follow-up (*m* 96.32; *SD* 2.58).

The respiratory rate was higher (18 breaths per minute) among patients in the live bedside music group compared to the control group (16 times per minute). We found no differences within the groups.

### *3.4 Anxiety*

In both groups, the median VAS score was zero at all test points, and no significant differences were found between the groups. A decrease in anxiety was noted between the pre-test and post-test or the follow-up test in both groups, as illustrated in Figure 1c. Furthermore, the level of anxiety range in the live bedside group as computed by VAS decreased considerably from 0–10 at the pre-test to 0–2.7 at the post-test, 0–2.2 at the follow-up.

## 4. Discussion

Findings from the present investigation gathered evidence to demonstrate that live music creates a positive environment and has a positive effect on the postoperative pain in the geriatric patients that lasts for at least three hours. The same effects were not found in the control group. To our best knowledge, no previous study has examined the effect of live music on pain, specifically in the elderly surgical population. This study also distinguishes itself by the fact that a prolonged decrease in pain perception, up to three hours after intervention, was found, despite

the low pain scores at baseline in both groups. The pain scores were reduced by 0.59 at post-test and 0.73 at follow-up; this is marginally greater than the results described in two meta-analyses evaluating recorded music interventions postoperatively with a standardized mean difference of 0.53/0.71 [21, 22].

In the present study, we used a VAS to measure pain, which is a commonly used instrument for this purpose in studies with similarly aged populations with recorded music [8, 10, 12, 14, 15, 17], However, it remains unclear whether these findings reflect a reduction in pain medication. Some of the earlier studies with recorded music yielded conflicting results in the reduction of pain medication [8, 12, 13, 23]. It is difficult to generalize the data due to the heterogeneity of our study population. Hence, the evidence-based effect of live music on drug use among the geriatric surgical population is still obscure. Further research is needed to establish the influence of live bedside music on pain, which is more pronounced in patients undergoing major surgery. The underlying mechanistic pathway also deserves further insight. Furthermore, it is necessary to understand and compare the effect of live music with recorded music to determine clinical implications and draw definite conclusions. The results from the present investigation indicate that live bedside music can be potentially used in pain management.

Although, due to the distribution of the data, the median score for anxiety was zero, there was a notable decrease in the range of the live bedside group, which was not present in the control group. This concords with previously conducted studies on elderly surgical patients with recorded music that found a positive effect on anxiety [8, 12, 14, 17]. This is relevant because psychological aspects such as anxiety can affect the postoperative pain of an older surgical patient and adversely affect a patient's recovery [24, 25].

Based on our data, music has some effect on psychological parameters, although its clinical relevance is debatable. Non-parametric analyses of the heart rate revealed a significant decrease between pre- and post-test values and pre- and follow-up test values, which was not found in studies with recorded music [10, 12-15, 26, 27]. It can be presumed that live music affects the autonomic nervous system. It is a well-acknowledged fact that the heart rate is regulated by the autonomic nervous system, where the parasympathetic nervous system pacifies the body after the action of the sympathetic nervous system. Heart rate increases when the sympathetic nervous system is activated as a response toward harmful stimuli like pain or surgery, and responses are monitored by calculating heart rate variability (HRV), which is the time difference between consecutive heartbeats [28]. Earlier studies [29, 30] revealed that live music not only enhances parasympathetic activity but also causes a reduction in sympathetic activity as measured by HRV. The influence of live music on HRV in elderly patients after surgery, to our best knowledge, has not been measured and should be further explored to gain insight into the mechanism behind the effect of live music.

This study was performed with live music and conducted among a broad range of elderly patients undergoing various types of major and complex surgery. The data were collected in both groups by the same professionals, any Hawthorne effect cannot be completely ruled out due to the nature of the intervention and focus on experienced pain of patients. The limited availability of the musicians restricted the inclusion of patients who were admitted at the same time. However, baseline characteristics between the live bedside music group and the control group did not differ.

In the Netherlands, music therapy is not common care in hospital wards, and certainly not in surgical wards. In a previously conducted review on the effect of live music in older patients, no

specific studies using live music therapy in surgical patients were found [18]. The intervention in our study was performed by professional musicians and must not be confused with music therapy, in which selected music-based interventions are applied using both music and the therapist-patient relationship as agents of change, or with 'music medicine', an intervention in which music is delivered by healthcare professionals [31]. In the analysis of pain perception, the effects of musical characteristics like volume, beats per minute, patient's choice of music, and various types of improvisations, were not taken in to account. Some studies among young adults have shown that personal preference and type of music played can be associated with the effect of music on pain perception [32, 33]. However, a meta-analysis by Hole and colleagues (2015) found a positive but non-significant effect of the music choice on reduction in pain [21]. Further research should be done keeping these variables into account.

The study demonstrates the applicability of live bedside music is an attractive and likely achievable option, which may create a new dimension in the working environment for professional musicians. The advantage of this intervention is that live music is multi-faceted and can be designed in various ways, which could be further explored. A larger-scale implementation and formal feasibility study can potentially bring out obstructing economic factors as attitudes of patients and healthcare professionals toward this innovative practice. Nevertheless, the results of this study indicate that live music influences pain perception in geriatric surgical patients in a positive way with no side effects.

## 5. Conclusion

Live bedside music, performed by professional musicians, has a positive effect on the perceived pain of elderly patients after surgery compared with patients who did not receive the intervention. Further research on the clinical implications, such as reduced pain medication usage, and the mechanism behind decreased pain must be conducted.

## Author Contributions

All authors contributed substantial, approved the final version and are accountable for all aspects.

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## Competing Interests

The authors have declared that no competing interests exist.

## References

1. Sommer M, de Rijke JM, van Kleef M, Kessels AGH, Peters ML, Geurts JWJM, et al. The prevalence of postoperative pain in a sample of 1490 surgical inpatients. Eur J Anaesthesiol. 2008; 25: 267-274.

2. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: The importance of pain and pain management. Anesth Analg. 2006; 102: 1267-1273.
3. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003; 97: 534-540.
4. Yorke J, Wallis M, McLean B. Patients' perceptions of pain management after cardiac surgery in an australian critical care unit. Heart Lung. 2004; 33: 33-41.
5. Faherty BS, Grier MR. Analgesic medication for elderly people post-surgery. Nurs Res. 1984; 33: 369-372.
6. American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009; 57: 1331-1346.
7. Oktora MP, Denig P, Bos JHJ, Schuiling-Veninga C, Hak E. Trends in polypharmacy and dispensed drugs among adults in the Netherlands as compared to the United States. PLoS One. 2019; 14: 1-15.
8. Bauer BA, Cutshall SA, Anderson PG, Prinsen SK, Wentworth LJ, Olney TJ, et al. Effect of the combination of music and nature sounds on pain and anxiety in cardiac surgical patients: A randomized study. Altern Ther Health Med. 2011; 17: 16-23.
9. Zimmerman L, Nieveen J, Barnason S, Schmaderer M. The effects of music interventions on postoperative pain and sleep in coronary artery bypass graft (CABG) patients. Sch Inq Nurs Pract. 1996; 10: 153-170; discussion 171-174.
10. Masuda T, Miyamoto K, Shimizu K. Effects of music listening on elderly orthopaedic patients during postoperative bed rest. Nord J Music Ther. 2005; 14: 4-14.
11. McCaffrey R, Locsin R. The effect of music on pain and acute confusion in older adults undergoing hip and knee surgery. Holist Nurs Pract. 2006; 20: 218-224; quiz 225-226.
12. Allred KD, Byers JF, Sole ML. The effect of music on postoperative pain and anxiety. Pain Manag Nurs. 2010; 11: 15-25.
13. Sendelbach SE, Halm MA, Doran KA, Miller EH, Gaillard P. Effects of music therapy on physiological and psychological outcomes for patients undergoing cardiac surgery. J Cardiovasc Nurs. 2006; 21: 194-200.
14. Lin PC, Lin ML, Huang LC, Hsu HC, Lin CC. Music therapy for patients receiving spine surgery. J Clin Nurs. 2011; 20: 960-968.
15. Vaajoki A, Kankkunen P, Pietila AM, Vehvilainen-Julkunen K. Music as a nursing intervention: Effects of music listening on blood pressure, heart rate, and respiratory rate in abdominal surgery patients. Nurs Health Sci. 2011; 13: 412-418.
16. Chaput-McGovern J, Silverman MJ. Effects of music therapy with patients on a post-surgical oncology unit: A pilot study determining maintenance of immediate gains. Arts Psychother. 2012; 39: 417-422.
17. Voss JA, Good M, Yates B, Baun MM, Thompson A, Hertzog M. Sedative music reduces anxiety and pain during chair rest after open-heart surgery. Pain. 2004; 112: 197-203.
18. van der Wal- Huisman H, Dons KSK, Smilde R, Heineman E, van Leeuwen BL. The effect of music on postoperative recovery in older patients: A systematic review. J Geriatr Oncol. 2018; 9: 550-559.

19. International Association for the Study of Pain. IASP Terminology. 2017, dec. 14; Available at: https://www.iasp-pain.org/terminology?navItemNumber=576. Accessed July, 17, 2019.
20. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: A critical review. Psychol Med. 1988; 18: 1007-1019.
21. Hole J, Hirsch M, Ball E, Meads C. Music as an aid for postoperative recovery in adults: A systematic review and meta-analysis. Lancet. 2015; 386: 1659-1671.
22. Kuhlmann AYR, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. Meta-analysis evaluating music interventions for anxiety and pain in surgery. Br J Surg. 2018; 105: 773-783.
23. Vaajoki A, Pietila AM, Kankkunen P, Vehvilainen-Julkunen K. Effects of listening to music on pain intensity and pain distress after surgery: An intervention. J Clin Nurs. 2012; 21: 708-717.
24. Muñoz Sastre MT, Albaret MC, Maria Raich Escursell R, Mullet E. Fear of pain associated with medical procedures and illnesses. Eur J Pain. 2006; 10: 57-66.
25. Twiss E, Seaver J, McCaffrey R. The effect of music listening on older adults undergoing cardiovascular surgery. Nurs Crit Care. 2006; 11: 224-231.
26. Barnason S, Zimmerman L, Nieveen J. The effects of music interventions on anxiety in the patient after coronary artery bypass grafting. Heart Lung. 1995; 24: 124-132.
27. Nilsson U. Soothing music can increase oxytocin levels during bed rest after open-heart surgery: A randomised control trial. J Clin Nurs. 2009; 18: 2153-2161.
28. McCraty R, Shaffer F. Heart rate variability: New perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. Glob Adv Health Med. 2015; 4: 46-61.
29. Shoda H, Adachi M, Umeda T. How live performance moves the human heart. PLoS One. 2016; 11: e0154322.
30. Kurita A, Takase B, Okada K, Horiguchi Y, Abe S, Kusama Y, et al. Effects of music therapy on heart rate variability in elderly patients with cerebral vascular disease and dementia. J Arrhythm. 2006; 22: 161-166.
31. Bradt J, Magee WL, Dileo C, Wheeler BL, McGilloway E. Music therapy for acquired brain injury. Cochrane Database Syst Rev. 2010. doi: 10.1002/14651858.CD006787.pub2.
32. Martin-Saavedra JS, Vergara-Mendez LD, Pradilla I, Vélez-van-Meerbeke A, Talero-Gutiérrez C. Standardizing music characteristics for the management of pain: A systematic review and meta-analysis of clinical trials. Complement Ther Med. 2018; 41: 81-89.
33. Mitchell LA, MacDonald RA. An experimental investigation of the effects of preferred and relaxing music listening on pain perception. J Music Ther. 2006; 43: 295-316.


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