Depressive symptoms and physical activity mediate the adverse effect of pain on functional independence in patients with arthritis: Evidence from the Canadian Longitudinal Study on Aging

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ABSTRACT

Objective. Arthritis is a chronic condition affecting hundreds of millions of people worldwide, often leading to pain and functional limitations. This study aimed to investigate the direct and indirect effects of pain on functional independence in individuals with arthritis. Depressive symptoms and physical activity were examined as potential mediators of this relationship.

Methods. A total of 6972 participants with arthritis (4930 with osteoarthritis and 694 with rheumatoid arthritis) were included from the Canadian Longitudinal Study on Aging. Multiple linear regression models, generalized linear models, and bootstrapping were used to assess the relationships between baseline pain, depressive symptoms, physical activity, and functional status at follow-up.

Results. Baseline pain was positively associated with depressive symptoms (b = 0.356 [95% CI: 0.310 to 0.402]) and negatively associated with physical activity (b = -0.083 [95% CI: -0.125 to -0.042]). Functional status at follow-up was significantly predicted by baseline pain (OR = 1.834 [95% CI: 1.306 to 2.610]), depressive symptoms (OR = 1.431 [95% CI: 1.205 to 1.709]), and physical activity (OR = 0.550 [95% CI: 0.440 to 0.683]). Mediation analysis showed that 30.4% of the effect of pain on functional status was mediated by the total indirect effect, with contributions from depressive symptoms (19.8%), physical activity (8.9%), and the serial mediation pathway (1.7%).

Conclusions. Pain at baseline was associated with a higher likelihood of functional dependence in basic and instrumental activities of daily living after a mean follow-up period of 6.3 years, with depressive symptoms and lower physical activity acting as partial mediators. These findings highlight the importance of managing pain, mental health, and physical activity in patients with arthritis to maintain functional independence.

Impact. These findings support the importance for intervention to target both mental health and exercise to mitigate functional decline resulting from the long-term effects of pain in patients with arthritis.

Keywords. Aged Adults; Cohort Studies; Depression; Exercise; Mental Health; Rheumatology

INTRODUCTION

The global prevalence of arthritis, particularly osteoarthritis, has risen significantly in recent decades, with cases increasing by 137% from 256 million in 1990 to 607 million in 2021[1]. If trends continue, projections indicate that 1 billion people will have osteoarthritis by 2050[2]. As a result, the burden of arthritis on society will continue to grow, since pain, a primary symptom, has been shown to predict functional decline[3-6].

Understanding the relationship between pain and functional status has important implications, as loss of independence significantly affects quality of life[7,8] and healthcare costs[9]. While pain directly contributes to functional decline[3-6], this effect may be mediated by factors related to mental and physical health. Two relevant candidate mediators of the relationship between pain and functional independence are depressive symptoms and physical activity, as both are influenced by pain[10-13] and predict functional independence[6,14,15]. Understanding the complex relationships between pain, depressive symptoms, and physical activity, and how they collectively influence functional independence in individuals with arthritis may inform targeted interventions in this population.

Depression is one of the most common comorbidities in arthritis, with recent meta-analyses suggesting that it affects approximately one-third of this population[16,17]. The relationship between pain and depressive symptoms has been consistently reported in the literature[18] and may be bidirectional[19]. Longitudinal studies investigating osteoarthritis have shown that greater pain symptoms prospectively predict the incidence of depression[20-22], while other studies have shown that depressive symptomology may exacerbate the experience of pain[23,24]. However, in the context of arthritis, the mechanistic explanations supporting the effect of pain on depression are stronger than those supporting the reverse, mainly because pain is a primary and more direct symptom resulting from joint inflammation, whereas depression is a comorbidity that develops secondary to the chronic pain.

The mediation of the effect of pain on functional status by depressive symptoms is well documented in the pain literature[25-32]. This literature includes studies focusing on back pain[25-28] and traumatic injury[29-31], but none have specifically examined individuals with arthritis. Instead, studies in arthritis populations have primarily examined a different mediation model, where functional status is the mediator and depressive symptoms are the outcome[33,34], a model more relevant to mental health professionals. From a rehabilitation perspective, the focus is rather on understanding the mechanisms that may improve functional outcomes. Moreover, conceptualizing depressive symptoms as a mediator of the effect of pain on functional status aligns with the biopsychosocial approach of pain in rehabilitation[35], emphasizing the importance of psychological factors in physical functioning. The mechanistic basis for this mediation model is well-supported, as depressive symptoms have been shown to lead to reduced motivation[36], increased fatigue[33,37,38], and avoidance behaviors[39], all of which can affect function[40]. However, to the best of our knowledge, this mediation model has not yet been evidenced in individuals with arthritis.

Another potential mediator of the effect of pain on functional status is physical activity in individuals with arthritis, as pain has been shown to predict physical activity levels[41], which in turn have been shown to improve physical functioning[42]. While this indirect effect through physical activity has recently been examined in individuals with back pain[43,44], this mediating effect has not been examined in individuals with arthritis. As physical activity has been shown to be an effective intervention for improving pain and function[45], refining our understanding of this

relationship, taking into account the influence of depressive symptoms, could further inform rehabilitation programs for patients with arthritis.

The aim of this study was to examine the relationship between pain and functional status in people with arthritis using the Canadian Longitudinal Study on Aging datasets. Specifically, we examined whether depressive symptoms and physical activity mediate the effect of baseline pain on functional status at follow-up. We hypothesized that pain status would have a direct effect on functional status. In addition, we hypothesized an indirect effect, whereby the presence of pain would be associated with higher depressive symptoms and lower physical activity levels, both of which would, in turn, predict higher odds of functional dependence, over and above the direct effect of pain.

METHODS

Participants

Participants were recruited in the Canadian Longitudinal Study on Aging (CLSA) through Canada's provincial health registries, random-digit dialing, and the Canadian Community Health Survey on Healthy Aging[46,47]. Exclusion criteria included: residents living in Canada's three territories and First Nations reserves, full-time members of the Canadian Armed Forces, people living with cognitive impairments, and individuals living in institutions, including 24-hour nursing homes[46]. All participants who had baseline measures of pain, depressive symptoms, physical activity, age, and sex, as well as measures of functional limitations at follow-up were included in the analyses.

Data of the 'baseline' assessment was collected between 2010 and 2015 using two approaches: data collection from a 'tracking' cohort of participants via 60-minute computer-assisted phone interviews and data collection from a 'comprehensive' cohort via 90-minute in-person interviews in addition to a data-collection site visit. Additionally, a 'maintaining contact questionnaire' was administered by phone to the comprehensive and tracking cohorts. The maintaining contact questionnaire, tracking cohort, and comprehensive cohort were used as baseline in our analyses. Between 2018 and 2021 another wave of data was collected during the follow-up assessment.

Variables

Arthritis

At the baseline assessment, participants self-reported whether they had ever been diagnosed with rheumatoid arthritis, osteoarthritis, or any other type of arthritis. Five single-item questions were used: "Has a doctor ever told you that you have [osteoarthritis in the knee / osteoarthritis in the hip / osteoarthritis in one or both hands / rheumatoid arthritis / any other type of arthritis]?". Responses were yes or no. The dataset was initially filtered to include individuals with any type of arthritis for the main analyses. In addition, sensitivity analyses were conducted on two specific subsets: one comprising individuals with osteoarthritis and the other consisting of those with rheumatoid arthritis.

Functional Status

Basic and instrumental activities of daily life (I/ADL) at baseline and follow-up were measured with a modified version of the Older Americans' Resources and Services Multidimensional Functional Assessment Questionnaire (OARS)[48,49]. Twenty questions were

asked to participants regarding their ability to complete seven basic activities of daily life (ADL) (e.g., can you eat without help, can you walk without help) in addition to 21 questions regarding seven instrumental activities of daily living (IADL) (e.g., can you use the telephone without help, can you prepare you own meals without help). The 'Basic and Instrumental Activities of Daily Living Classification' is a derived variable in the CLSA dataset that produces the following scores: 1 (no functional limitations), 2 (mild functional limitations), 3 (moderate functional limitations), 4 (severe functional limitations), and 5 (total functional limitations). The method used to derive this variable assigns extra weight to the ability to prepare meals and was scored to be similar to variables used in Statistics Canada's Canadian Community Health Survey[50]. A binary variable of the Basic and Instrumental Activities of Daily Living Classification was computed for measures assessed at baseline and follow-up assessment. These variables classify participants with no or mild functional limitations as functionally independent and participants with moderate, severe, or total functional limitations as functionally dependent.

Pain

Pain status was assessed with the question "Are you usually free of pain or discomfort?". Responses were yes or no.

Depression Symptoms

The Center for Epidemiological Studies Short Depression Scale (CESD-10)[51] was used to assess depressive symptoms at baseline. The CESD-10 contains 10 items measuring depressive feelings, restless sleep, hopefulness for the future, and loneliness (e.g., "How often did you feel hopeful about the future?"; "How often did you feel that everything you did was an effort?"). Response options range from 3 ["All of the time (5-7days)"] to 0 ["Rarely or never (less than 1 day)"]. A sum score ranging from 0-30 was used in the analyses. When one response is missing, CLSA imputes the value using the mean of the remaining nine items to compute the sum score. The distribution for the CESD-10 was highly skewed and a log-transformed version of the variable was used in the analyses.

Physical Activity

Physical activity and sedentary behaviour were measured at baseline as independent behaviours with the Physical Activity Scale for the Elderly (PASE)[52], which assesses the frequency of sedentary behaviour, walking, light physical activity, moderate physical activity, strenuous physical activity, and exercise. Items asked participants to report on their activity levels over the previous 7 days on a 1 (never) to 4 (often, 5-7 days) scale and to indicate the time per day engaged in each of these activities on a 1 (less than 30 minutes) to 5 (four hours or more) scale. A total physical activity score was derived from these items according to the PASE administration and scoring instruction manual[53], resulting in scores from 0 to 485, with higher scores indicating higher levels of physical activity.

Statistical Analyses

All analyses were conducted in R version 4.4.1[54] and analysis scripts are freely available[55]. We conducted a mediation analysis to examine the direct and indirect effects of pain on functional status, considering depressive symptoms and physical activity as mediators. Functional status was assessed during the follow-up survey (2018-2021), while all the other variables were collected during the baseline assessment (2011-2015). The mediation analysis was conducted using Process

Variables	Any Arthritis (n = 6972) Count (%) or Mean (SD)	Osteoarthritis (n = 4930) Count (%) or Mean (SD)	Rheumatoid Arthritis (n = 694) Count (%) or Mean (SD)
Pain			
No Pain	3288 (47.2%)	2229 (45.2%)	270 (38.9%)
Pain	3684 (52.8%)	2701 (54.8%)	424 (61.1%)
Physical Activity	185.0 (75.8)	180.2 (76.0)	190.9 (75.7)
Depressive Symptoms	5.5 (4.6)	5.5 (4.7)	5.9 (4.8)
Sex			
Male	2882 (41.3%)	1943 (39.4%)	280 (40.3%)
Female	4090 (58.7%)	2987 (60.6%)	414 (59.7%)
Age Group			
45-54 years	1720 (24.7%)	1002 (20.3%)	207 (29.8%)
55-64 years	2612 (37.5%)	1858 (37.7%)	236 (34.0%)
65-74 years	1698 (24.4%)	1332 (27.0%)	169 (24.4%)
75-85 years	942 (13.5%)	738 (15.0%)	82 (11.8%)
Functional Limitations			
None	6310 (90.5%)	4417 (89.6%)	614 (88.5%)
Mild	611 (8.8%)	473(9.6%)	71 (10.2%)
Moderate	43(0.6%)	34 (0.7%)	5 (0.7%)
Severe	5 (0.1%)	4 (0.1%)	2 (0.3%)
Total	3 (.05%)	2 (.05%)	2 (0.3%)

Table 1. Sample characteristics at baseline by arthritis type

for R[56] (Model 6), which allows for serial mediation modeling. The model included pain as the independent variable (binary: 0 = no pain, 1 = pain) and functional status as the dependent variable (binary: 0 = functionally independent, 1 = functionally dependent). Depressive symptoms and physical activity were included as mediators, both measured as continuous variables. Sex (binary: 0 = male, 1 = female) and age (continuous) were included as covariates to account for potential confounding effects. Continuous variables were standardized.

First, we estimated the direct effect of baseline pain on functional status at follow-up using a logistic regression model, adjusting for sex and age. Then, we examined the effect of pain on depressive symptoms using a multiple linear regression model. A second multiple linear regression model was then used to examine whether depressive symptoms predicted physical activity. Finally, a logistic regression model was used to assess the direct effects of baseline pain, depressive symptoms, and physical activity on functional status at follow-up. Standardized beta regression coefficients (b) and 95% confidence intervals (95% CI) were reported for linear regression models. The 'tidy' function of the 'broom' package[57] was used to transform logistic regression outputs (log odds ratios) into odds ratios and to compute their 95% CI. For direct effects, statistical significance was assessed using a two-tailed α level of 0.05. The proportion of the effect of baseline pain on functional status mediated by the mediators was calculated using the difference in log odds ratios

(log OR) between the models with and without the mediators: ($\log(OR_{\text{without mediators}}) - \log(OR_{\text{with mediators}})) / \log(OR_{\text{with mediators}})$.

The total indirect effect of pain on functional status was estimated by summing three individual indirect pathways: the pathway through depressive symptoms, the pathway through physical activity, and the serial pathway involving both mediators. Bootstrapping (5,000 resamples) was used to estimate log odds ratios of the indirect effects and their 95% CI. The significance of the indirect effects was determined by whether the 95% bootstrapped confidence interval excluded zero.

Sensitivity Analyses

Three sensitivity analyses were conducted to assess the robustness of our results. The first sensitivity analysis used a different binary classification of functional status at follow-up, classifying participants with no functional limitations as functionally independent and those with mild, moderate, severe, or total functional limitations as functionally dependent. The second sensitivity analysis focused on participants with osteoarthritis. The third sensitivity analysis focused on participants with rheumatoid arthritis.

RESULTS

Descriptive Results

A total of 6972 participants reported having arthritis, including 4930 with osteoarthritis, and 694 with rheumatoid arthritis. Among the 6,972 participants with any type of arthritis (Table 1), baseline data showed that 58.7% were female, more than half of them reported experiencing pain (52.8%), the mean physical activity score was 185.0 ± 75.8, and the mean depression score was 5.5 ± 4.6. The majority (90.5%) reported no functional limitations, while 8.8% had mild limitations, and fewer than 1% had moderate or severe limitations. Most participants were aged 55–64 years (37.5%), followed by those aged 45–54 years (24.7%) and 65–74 years (24.4%), with the smallest proportion in the 75–85 age group (13.5%). The distribution of demographic and clinical characteristics for participants with osteoarthritis and rheumatoid arthritis is presented in Table 1. The average time between baseline and follow-up measures was 6.3 ± 0.8 years, with a range of 4.0 to 9.6 years.

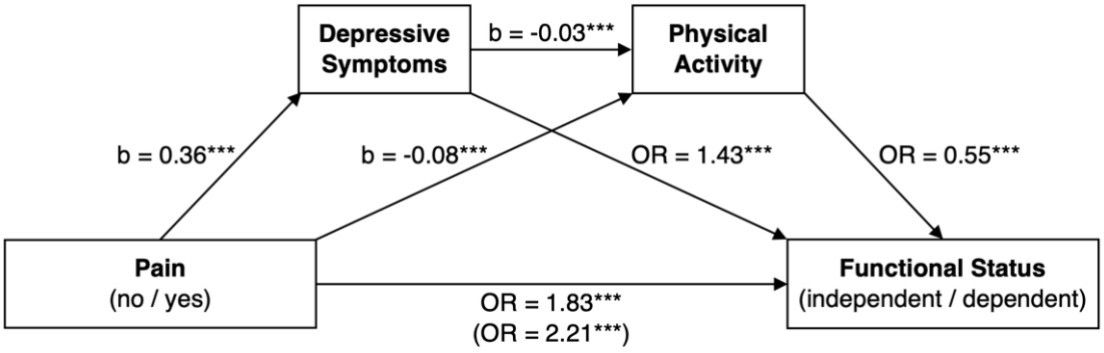

Figure 1. Direct effects of the mediation analysis. b = beta, OR = Odds ratio, ***p<.001

Main Analyses

We used multiple linear regression models, generalized linear models, and bootstrapping to investigate the direct and indirect effects of baseline pain on functional status 6.3 ± 0.8 years later. Depressive symptoms and physical activity were examined as potential mediators. The analysis controlled for covariates of sex; age, and baseline functional status, and was based on a sample 6972 participants with any type of arthritis.

Depressive Symptoms (Mediator 1)

The first stage of the mediation model examined the effect of baseline pain on the first mediator: Depression. The multiple linear regression model explained 4.7% of the variance in depressive symptoms (adjusted $R^2 = 0.047$). Results showed a positive association between pain and depressive symptoms (b = 0.356 [95% CI: 0.310 to 0.402]; $P < 2.0 \times 10^{-16}$) (Fig. 1). Males exhibited fewer depressive symptoms than females (b = -0.136 [95% CI: -0.183 to -0.089]; $P = 1.1 \times 10^{-8}$). Older participants reported lower levels of depression than younger ones (b = -0.072 [95% CI: -0.095 to -0.049]; $P = 8.0 \times 10^{-10}$). Baseline functional status was associated with depressive symptoms (b = 0.723 [95% CI: 0.453 to 0.992]; $P = 1.5 \times 10^{-7}$).

Physical Activity (Mediator 2)

The second stage of the mediation examined the effect of pain and depression on the second mediator: Physical activity. The multiple linear regression model accounted for 25.3% of the variance in physical activity (adjusted $R^2 = 0.253$). Results showed that pain (b = -0.083 [95% CI: -0.125 to -0.042]; $P = 8.0 \times 10^{-5}$) and depressive symptoms (b = -0.030 [95% CI: -0.050 to -0.009]; $P = .005$) were negatively associated with physical activity (Fig. 1). Males exhibited higher levels of physical activity than females (b = 0.401 [95% CI: 0.360 to 0.443]; $P < 2.0 \times 10^{-16}$). Older participants reported lower levels of physical activity than younger ones (b = 0.450 [95% CI: -0.470 to -0.430]; $P < 2.0 \times 10^{-16}$). Baseline functional status was associated with physical activity (b = -0.743 [95% CI: -0.983 to -0.505]; $P = 1.1 \times 10^{-9}$).

Direct and Indirect Effects on Functional Status (Outcome)

The third stage of the mediation examined the effect of pain, depression, and physical activity on the outcome: functional status. The generalized linear model accounted for 18.0% of the variance in functional status (McFadden's $R^2 = 0.180$). Results showed a direct effect of baseline pain on functional status at follow-up (log OR = 0.607; OR = 1.834 [95% CI: 1.306 to 2.610]; $P = 5.8 \times 10^{-4}$) (Fig. 1), indicating that participants with pain had higher odds of being functionally dependent 4.0 to 9.6 years compared to those without pain. Similarly, depressive symptoms and physical activity were significant predictors of functional status (Fig. 1). Baseline depressive symptoms increased the odds of being dependent at follow-up (OR = 1.431 [95% CI: 1.205 to 1.709]; $P = 5.7 \times 10^{-5}$), whereas baseline physical activity reduced the odds (OR = 0.550 [95% CI: 0.440 to 0.683]; $P = 9.4 \times 10^{-8}$). Older participants had higher odds of being functionally dependent at follow-up than younger ones (OR = 1.896 [95% CI: 1.595 to 2.261]; $P = 6.6 \times 10^{-13}$). Results showed no evidence of an effect of sex (OR = 0.991 [95% CI: 0.703 to 1.385]; $P = .958$). Baseline functional status predicted functional status at follow-up (b = 17.923 [95% CI: 9.513 to 33.740]; $P < 2.0 \times 10^{-16}$).

When both mediators were not included in the model, the odds ratio of pain on functional status was higher (log OR = 0.791; OR = 2.205 [95% CI: 1.581 to 3.119]; $P = 4.8 \times 10^{-6}$) (Fig. 1). The difference in the log OR between the models with and without both mediators showed that

30.4% of the effect of baseline pain on functional status was mediated by the total indirect effect of the mediators (depressive symptoms and physical activity). When removing one mediator at a time from the model, the difference in the log OR showed that 19.8% of the effect was mediated by depressive symptoms and 8.9% by physical activity, suggesting that 1.7% was explained by the serial mediation of depressive symptoms and physical activity.

Bootstrapping analysis showed a total indirect effect of baseline pain on functional status at follow-up (log OR = 0.184 [95% CI: 0.110 to 0.267]) (Fig. 2), which was partitioned into three indirect pathways: through depressive symptoms (log OR = 0.128 [95% CI: 0.066 to 0.200]), through physical activity (log OR = 0.050 [95% CI: 0.019 to 0.090]), and through a serial pathway including depression followed by physical activity (log OR = 0.006 [95% CI: 0.001 to 0.013]). The serial pathway in which physical activity was the first mediator and depressive symptoms the second was also explored and yielded similar results (log OR = 0.0013 [95% CI: 0.0003 to 0.0028]). Since bootstrapping was used to examine these indirect effects, confidence interval is considered a more reliable indicator of statistical significance. The fact that zero is not included in any of the bootstrapped 95% CI indicates that all these indirect effects are statistically significant.

Sensitivity Analyses

Different classification of functional status

The sensitivity analysis that classified participants with mild functional limitations as functionally independent (n = 6972) rather than functionally dependent, yielded results similar to those of the main analyses. Bootstrapping analysis showed a total indirect effect of baseline pain on functional status at follow-up (log OR= 0.152 [95% CI: 0.117 to 0.189]), which was partitioned into three indirect pathways: through depressive symptoms (log OR = 0.120 [95% CI: 0.089 to 0.154]), through physical activity (log OR = 0.028 [95% CI: 0.013 to 0.046]), and through a serial pathway including depression and physical activity (log OR = 0.004 [95% CI: 0.001 to 0.007]). The fact that zero is not included in any of the bootstrapped 95% CI indicates that all these indirect effects are statistically significant.

Osteoarthritis

Results of the sensitivity analysis focusing on participants with osteoarthritis (n = 4930) were similar to those of the main analyses. Bootstrapping analysis showed a total indirect effect of baseline pain on functional status at follow-up (log OR = 0.203 [95% CI: 0.113 to 0.307]), which was partitioned into three indirect pathways: through depressive symptoms (log OR = 0.139 [95% CI: 0.062 to 0.227]), through physical activity (log OR = 0.055 [95% CI: 0.016 to 0.109]), and through a serial pathway including depression and physical activity (log OR = 0.009 [95% CI: 0.002 to 0.019]). The fact that zero is not included in any of the bootstrapped 95% CI indicates that all these indirect effects are statistically significant.

Rheumatoid Arthritis

Results of the sensitivity analysis focusing on participants with rheumatoid arthritis (n = 694) suggested that the total mediation (log OR = 0.250 [95% CI: 0.049 to 0.574]) was primarily driven by the pathway through depressive symptoms (log OR = 0.185 [95% CI: 0.013 to 0.453]) as the pathway through physical activity (log OR = 0.055 [95% CI: -0.089 to 0.226]) and the serial mediation pathway through both depressive symptoms and physical activity (log OR = 0.010 [95% CI: -0.013 to 0.038]) had bootstrapped 95% CI that included zero, indicating that these indirect effects were not statistically significant.

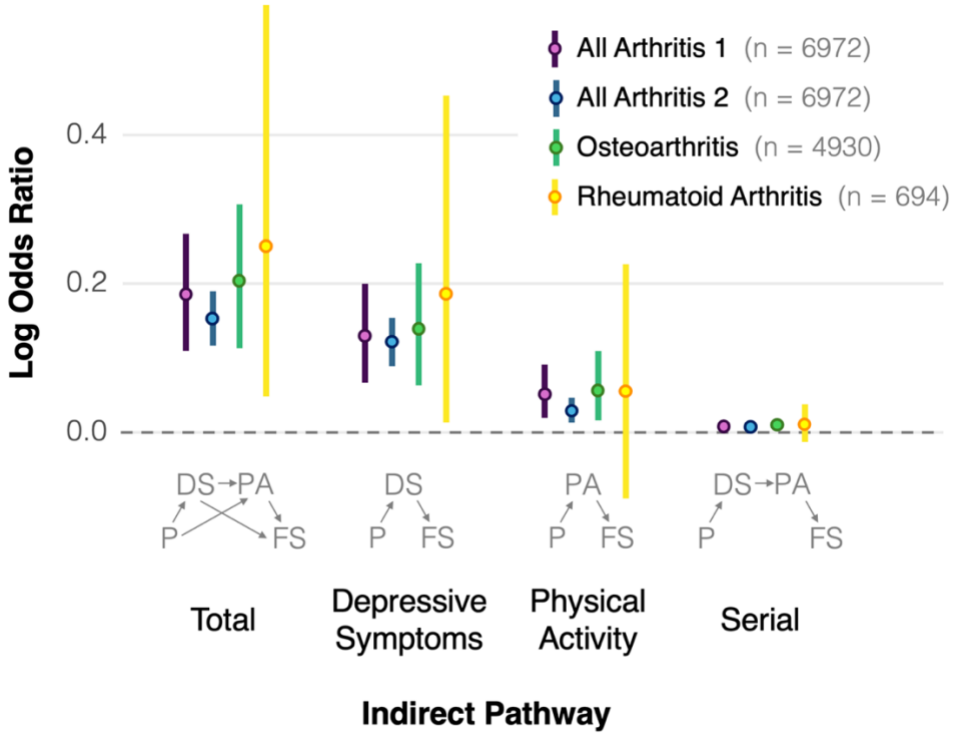

Figure 2. Indirect effects of baseline pain on functional status at follow-up based on bootstrapping analysis. The total indirect effect is partitioned into three indirect pathways: through depressive symptoms (P→DS→FS), through physical activity (P→PA→FS), and through a serial pathway including depression and physical activity (P→DS→PA→FS). The horizontal dotted line at 0 indicates no effect, the dots represent estimated log odds ratios, and the vertical lines represent 95% confidence interval for each estimate. The indirect effects are presented for the main analysis that included participants with any type of arthritis who were classified as functionally independent if they had no or mild functional limitations and as functionally dependent if they had moderate, severe, or total functional limitations (All Arthritis 1) and for the three sensitivity analyses: participants with no functional limitations classified as functionally independent and those with mild, moderate, severe, or total functional limitations as functionally dependent (All Arthritis 2), participants with osteoarthritis, and participants with rheumatoid arthritis. P = pain, DS = depressive symptoms, PA = physical activity, FS = functional status.

DISCUSSION

Main Findings

This study examined depressive symptoms and physical activity as potential mediators of the longitudinal relationship between baseline pain and functional status over a mean follow-up of 6.3 years in people with arthritis. Our results provide empirical support for a significant direct effect of baseline pain on future functional dependence in ADLs and IADLs, as well as an indirect effect through both depressive symptoms and physical activity. Consistent with the biopsychosocial approach to pain in rehabilitation[35], these findings highlight the importance of addressing both psychological and behavioral pathways in rehabilitation programs for patients with arthritis.

Comparison With the Literature

Our results indicate that individuals experiencing pain at baseline had higher odds of functional dependence at follow-up, while adjusting for sex, age, and baseline functional status. This direct association between baseline pain and future functional dependence aligns with previous research demonstrating that pain is a key determinant of disability in individuals with arthritis[3-6]. Taken together, these results suggests that early pain management may be critical in preventing long-term declines in functional abilities of individuals with arthritis.

Depressive symptoms were found to mediate the relationship between pain and functional status, accounting for 19.8% of the total mediation effect. Specifically, our results suggest that individuals with higher pain levels at baseline were more likely to experience depressive symptoms, which in turn increased the odds of functional dependence at follow-up. These results are consistent with those from studies of low back pain and post-traumatic pain that have documented the mediating role of depressive symptoms in the relationship between pain and functional status[25-32]. Importantly, our findings extend this evidence to individuals with arthritis, highlighting the broader relevance of these mechanisms across pain-related conditions. As depression is both modifiable and treatable, these findings suggest that rehabilitation professionals should consider mental health when implementing interventions aimed at pain-related functional decline in individuals with arthritis.

Physical activity was also a mediator, but to a lesser extent than depressive symptoms, accounting for 8.9% of the indirect effect of pain on functional status. This finding is consistent with studies showing similar indirect effects in individuals with low back pain[43,44]. Importantly, our findings extend this evidence to individuals with arthritis, reinforcing the importance of physical activity in maintaining functional independence. In addition, these findings suggest that exercise therapy should be considered as a component of rehabilitation programs aimed at restoring or preserving ADL and IADL independence in individuals with arthritis.

The mediation analysis also revealed a small but significant serial pathway in which depressive symptoms contributed to lower physical activity, which in turn affected functional status. Although this serial effect accounted for only 1.7% of the total mediation, it suggests that individuals who develop depressive symptoms due to pain may subsequently reduce their physical activity, further exacerbating their risk of functional decline.

Our sensitivity analyses confirmed the robustness of our findings across different functional status classifications and arthritis subtypes. The mediation effects were similar when classifying participants with mild functional limitations as functionally independent, reinforcing the validity of the main results. Additionally, analyses restricted to participants with osteoarthritis showed comparable mediation patterns, suggesting that the observed effects apply to the most common form of arthritis. However, in rheumatoid arthritis, the mediation effect was primarily driven by depressive symptoms, while the indirect effects through physical activity and the serial pathway were not statistically significant. This may indicate that the mechanisms linking pain to functional decline differ between arthritis subtypes, warranting further investigation.

Strengths and Limitations

This study has several strengths, including a large sample size of 6972 participants, a long follow-up period ranging from 4.0 to 9.6 years after baseline, and the use of multiple mediation analyses with bootstrapping to robustly estimate indirect effects. Several limitations should also be noted. First, the outcome and mediator variables were self-reported, which may have introduced

measurement bias, but is also inherent in large cohort studies. Second, despite adjusting for key confounders, unmeasured variables such as medication use, disease severity, and comorbidities could have influenced the results. Finally, although mediation analysis provides insight into potential causal pathways, the observational nature of the study precludes definitive causal conclusions.

Conclusion

This study provides evidence that pain contributes to long-term functional dependence both directly and indirectly through depressive symptoms and physical activity. The direct effect shows that individuals reporting pain have higher odds of being functionally dependent in ADLs and IADLs compared to those without pain. In addition, depressive symptoms and physical activity mediate this relationship, with depressive symptoms playing a more substantial role.

Our findings underscore the need for a comprehensive approach to arthritis care that goes beyond pain management alone. They suggest that interventions should include strategies to address depressive symptoms and promote physical activity to mitigate the long-term impact of pain on functional independence. A biopsychosocial framework that integrates physical, psychological, and behavioral components may provide a more effective approach to maintaining, restoring, or improving function in individuals with arthritis.

ARTICLE INFORMATION

Author Contributions

Based on the Contributor Roles Taxonomy (CRediT)[58], individual author contributions to this work are as follows: Miriam Goubran: Conceptualization, Writing (Original Draft), Writing (Review and Editing); Zachary M. van Allen: Methodology, Data Curation, Formal Analysis, Writing (Original Draft), Writing (Review and Editing); Martin Bilodeau: Conceptualization, Writing (Review and Editing), Supervision (MG), Project Administration; Matthieu P. Boisgontier: Conceptualization (Lead), Methodology, Data Curation, Formal Analysis, Visualization, Writing (Original Draft) (Lead), Writing (Review and Editing), Supervision (MG and ZMvA), Project Administration, Funding Acquisition.

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Data and Code Sharing

In accordance with good research practices[59], the R scripts used to analyse the data are publicly available in Zenodo[55]. This research was made possible using the data collected by the Canadian Longitudinal Study on Aging (CLSA) and was conducted using the CLSA Baseline Comprehensive Dataset version 7.0, Follow-Up 1 Comprehensive Dataset version 5.0, and Follow-

Up 2 Comprehensive dataset version 2.0 under application number 2304015. This dataset is available for researchers who meet the criteria (www.clsa-elcv.ca).

Disclaimer

The opinions expressed in this manuscript are the author's own and do not reflect the views of the Canadian Longitudinal Study on Aging.

REFERENCES

1. Qiao L, Li M, Deng F, et al. Epidemiological trends of osteoarthritis at the global, regional, and national levels from 1990 to 2021 and projections to 2050. *medRxiv.* 2024. https://doi.org/10.1101/2024.06.30.24309697
2. GBD 2021 Osteoarthritis Collaborators. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Rheumatol.* 2023;5(9):e508-e522. https://doi.org/10.1016/S2665-9913(23)00163-7
3. Sharma L, Cahue S, Song J, Hayes K, Pai YC, Dunlop D. Physical functioning over three years in knee osteoarthritis: role of psychosocial, local mechanical, and neuromuscular factors. *Arthritis Rheum*. 2003;48(12):3359-3370. https://doi.org/10.1002/art.11420
4. van Dijk GM, Veenhof C, Spreeuwenberg P, et al. Prognosis of limitations in activities in osteoarthritis of the hip or knee: a 3-year cohort study. *Arch Phys Med Rehabil*. 2010;91(1):58-66. https://doi.org/10.1016/j.apmr.2009.08.147
5. Pisters MF, Veenhof C, van Dijk GM, Heymans MW, Twisk JW, Dekker J. The course of limitations in activities over 5 years in patients with knee and hip osteoarthritis with moderate functional limitations: risk factors for future functional decline. *Osteoarthritis Cartilage*. 2012;20(6):503-510. https://doi.org/10.1016/j.joca.2012.02.002
6. van Allen ZM, Boisgontier MP. Prospective classification of functional dependence: insights from machine learning and the Canadian Longitudinal Study on Aging. *medRxiv.* 2024. https://doi.org/10.1101/2024.07.15.24310429
7. Araujo IL, Castro MC, Daltro C, Matos MA. Quality of life and functional independence in patients with osteoarthritis of the knee. *Knee Surg Relat Res.* 2016;28(3):219-224. https://doi.org/10.5792/ksrr.2016.28.3.219
8. Sieber S, Roquet A, Lampraki C, Jopp DS. Multimorbidity and quality of life: the mediating role of ADL, IADL, loneliness, and depressive symptoms. *Innov Aging*. 2023;7(4):1-13. https://doi.org/10.1093/geroni/igad047
9. Falck RS, Percival AG, Tai D, Davis JC. International depiction of the cost of functional independence limitations among older adults living in the community: a systematic review and cost-of-impairment study. *BMC Geriatr.* 2022;22(1):815. https://doi.org/10.1186/s12877-022-03466-w
10. Angst F, Benz T, Lehmann S, et al. Extended overview of the longitudinal pain-depression association: A comparison of six cohorts treated for specific chronic pain conditions. *J Affect Disord*. 2020;273:508-516. https://doi.org/10.1016/j.jad.2020.05.044
11. Wilcox S, Der Ananian C, Abbott J, et al. Perceived exercise barriers, enablers, and benefits among exercising and nonexercising adults with arthritis: results from a qualitative study. *Arthritis Rheum*. 2006;55(4):616-627. https://doi.org/10.1002/art.22098

12. Petursdottir U, Arnadottir SA, Halldorsdottir S. Facilitators and barriers to exercising among people with osteoarthritis: a phenomenological study. *Phys Ther.* 2010;90(7):1014-1025. https://doi.org/10.2522/ptj.20090217
13. Gay C, Eschalier B, Levyckyj C, Bonnin A, Coudeyre E. Motivators for and barriers to physical activity in people with knee osteoarthritis: a qualitative study. *Joint Bone Spine.* 2018;85(4):481-486. https://doi.org/10.1016/j.jbspin.2017.07.007
14. Boisgontier MP, Orsholits D, von Arx M, et al. Adverse childhood experiences, depressive symptoms, functional dependence, and physical activity: a moderated mediation model. *J Phys Act Health*. 2020;17(8):790-799. https://doi.org/10.1123/jpah.2019-0133
15. Penninx BW, Messier SP, Rejeski WJ, et al. Physical exercise and the prevention of disability in activities of daily living in older persons with osteoarthritis. *Arch Intern Med*. 2001;161(19):2309-2316. https://doi.org/10.1001/archinte.161.19.2309
16. Merry Del Val B, Shukla SR, Oduoye MO, Nsengiyumva M, Tesfaye T, Glinkowski WM. Prevalence of mental health disorders in knee osteoarthritis patients: a systematic review and meta-analysis. *Ann Med Surg*. 2024;86(8):4705-4713. https://doi.org/10.1097/MS9.0000000000002258
17. Hill J, Harrison J, Christian D, et al. The prevalence of comorbidity in rheumatoid arthritis: a systematic review and meta-analysis. *Br J Community Nurs*. 2022;27(5):232-241. https://doi.org/10.12968/bjcn.2022.27.5.232
18. Fonseca-Rodrigues D, Rodrigues A, Martins T, et al. Correlation between pain severity and levels of anxiety and depression in osteoarthritis patients: a systematic review and meta-analysis. *Rheumatology*. 2021;61(1):53-75. https://doi.org/10.1093/rheumatology/keab512
19. Kroenke K, Wu J, Bair MJ, Krebs EE, Damush TM, Tu W. Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care. *J Pain*. 2011;12(9):964-973. https://doi.org/10.1016/j.jpain.2011.03.003
20. Sayre EC, Esdaile JM, Kopec JA, et al. Specific manifestations of knee osteoarthritis predict depression and anxiety years in the future: Vancouver Longitudinal Study of Early Knee Osteoarthritis. *BMC Musculoskelet Disord*. 2020;21(1):467. https://doi.org/10.1186/s12891-020-03496-8
21. Zheng S, Tu L, Cicuttini F, et al. Depression in patients with knee osteoarthritis: risk factors and associations with joint symptoms. *BMC Musculoskelet Disord*. 2021;22(1):40. https://doi.org/10.1186/s12891-020-03875-1
22. Li M, Nie Y, Zeng Y, et al. The trajectories of depression symptoms and comorbidity in knee osteoarthritis subjects. *Clin Rheumatol*. 2022;41(1):235-243. https://doi.org/10.1007/s10067-021-05847-9
23. Rathbun AM, Stuart EA, Shardell M, Yau MS, Baumgarten M, Hochberg MC. Dynamic effects of depressive symptoms on osteoarthritis knee pain. *Arthritis Care Res*. 2018;70(1):80-88. https://doi.org/10.1002/acr.23239
24. Jacobs CA, Vranceanu AM, Thompson KL, Lattermann C. Rapid progression of knee pain and osteoarthritis biomarkers greatest for patients with combined obesity and depression: data from the Osteoarthritis Initiative. *Cartilage*. 2020;11(1):38-46. https://doi.org/10.1177/1947603518777577
25. Hall AM, Kamper SJ, Maher CG, Latimer J, Ferreira ML, Nicholas MK. Symptoms of depression and stress mediate the effect of pain on disability. *Pain*. 2011;152(5):1044-1051. https://doi.org/10.1016/j.pain.2011.01.014

26. Seekatz B, Meng K, Faller H. Depressivity as mediator in the fear-avoidance model: a path analysis investigation of patients with chronic back pain [German]. *Schmerz*. 2013;27(6):612-618. https://doi.org/10.1007/s00482-013-1376-0
27. Marshall PWM, Schabrun S, Knox MF. Physical activity and the mediating effect of fear, depression, anxiety, and catastrophizing on pain related disability in people with chronic low back pain. *PLoS One*. 2017;12(7):e0180788. https://doi.org/10.1371/journal.pone.0180788
28. Garcia AN, Cook CE, Gottfried O. Psychological, mobility, and satisfaction variables mediate the relationship between baseline back pain intensity and long-term outcomes in individuals who underwent lumbar spine surgery. *Musculoskelet Sci Pract*. 2021;55:102424. https://doi.org/10.1016/j.msksp.2021.102424
29. Wegener ST, Castillo RC, Haythornthwaite J, MacKenzie EJ, Bosse MJ; LEAP Study Group. Psychological distress mediates the effect of pain on function. *Pain*. 2011;152(6):1349-1357. https://doi.org/10.1016/j.pain.2011.02.020
30. Ross C, Juraskova I, Lee H, et al. Psychological distress mediates the relationship between pain and disability in hand or wrist fractures. *J Pain*. 2015;16(9):836-843. https://doi.org/10.1016/j.jpain.2015.05.007
31. Talaei-Khoei M, Fischerauer SF, Jha R, Ring D, Chen N, Vranceanu AM. Bidirectional mediation of depression and pain intensity on their associations with upper extremity physical function. *J Behav Med*. 2018;41(3):309-317. https://doi.org/10.1007/s10865-017-9891-6
32. Probst T, Neumeier S, Altmeppen J, Angerer M, Loew T, Pieh C. Depressed mood differentially mediates the relationship between pain intensity and pain disability depending on pain duration: a moderated mediation analysis in chronic pain patients. *Pain Res Manag*. 2016;2016:3204914. https://doi.org/10.1155/2016/3204914
33. Hawker GA, Gignac MA, Badley E, et al. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. *Arthritis Care Res*. 2011;63(10):1382-1390. https://doi.org/10.1002/acr.20298
34. Wang Q, Jayasuriya R, Man WY, Fu H. Does functional disability mediate the pain-depression relationship in older adults with osteoarthritis? A longitudinal study in China. *Asia Pac J Public Health*. 2015;27(2):NP382-NP391. https://doi.org/10.1177/1010539512443974
35. Smart KM. The biopsychosocial model of pain in physiotherapy: past, present and future. Phys Ther Rev. 2023;28(2):61-70. https://doi.org/10.1080/10833196.2023.2177792
36. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci Biobehav Rev*. 2011;35(3):537-555. https://doi.org/10.1016/j.neubiorev.2010.06.006
37. Katz P. Fatigue in rheumatoid arthritis. *Curr Rheumatol Rep*. 2017;19(5):25. https://doi.org/10.1007/s11926-017-0649-5
38. Fawole HO, Riskowski JL, Dell'Isola A, et al. Determinants of generalized fatigue in individuals with symptomatic knee osteoarthritis: the MOST Study. *Int J Rheum Dis*. 2020;23(4):559-568. https://doi.org/10.1111/1756-185X.13797
39. Cijs B, Stekelenburg R, Veenhof C, et al. Prognostic factors and changes in pain, physical functioning, and participation in patients with hip and/or knee osteoarthritis: a systematic review. Arthritis Care Res. 2025;77(2):228-239. https://doi.org/10.1002/acr.25428
40. Torlinska B, Raza K, Filer A, et al. Predictors of quality of life, functional status, depression and fatigue in early arthritis: comparison between clinically suspect arthralgia, unclassified

arthritis and rheumatoid arthritis. *BMC Musculoskelet Disord*. 2024;25(1):307. https://doi.org/10.1186/s12891-024-07446-6

41. Burrows NJ, Barry BK, Sturnieks DL, Booth J, Jones MD. The relationship between daily physical activity and pain in individuals with knee osteoarthritis. *Pain Med*. 2020;21(10):2481-2495. https://doi.org/10.1093/pm/pnaa096
42. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med. 2015;49(24):1554-1557. https://doi.org/10.1136/bjsports-2015-095424
43. Ekediegwu EC, Onwukike CV Onyeso OK. Pain intensity, physical activity, quality of life, and disability in patients with mechanical low back pain: a cross-sectional study. *Bull Fac Phys Ther*. 202429:1. https://doi.org/10.1186/s43161-023-00167-2
44. Karklins AE, Pernaa KI, Saltychev M, Juhola JE, Arokoski JPA. Physical activity as mediator between back pain and disability. *Int J Rehabil Res*. 2024;47(3):192-198. https://doi.org/10.1097/MRR.0000000000000638
45. Goh SL, Persson MSM, Stocks J, et al. Efficacy and potential determinants of exercise therapy in knee and hip osteoarthritis: a systematic review and meta-analysis. *Ann Phys Rehabil Med*. 2019;62(5):356-365. https://doi.org/10.1016/j.rehab.2019.04.006
46. Raina PS, Wolfson C, Kirkland SA. *Canadian Longitudinal Study on Aging (CLSA) Protocol*. 2009. Available from: https://clsa-elcv.ca/doc/511
47. Wolfson C, Raina PS, Kirkland SA, et al. The Canadian community health survey as a potential recruitment vehicle for the Canadian longitudinal study on aging. *Can J Aging*. 2009;28:243-249. https://doi.org/10.1017/S071498080999003
48. Fillenbaum GG. *Multidimensional functional assessment of older adults: The Duke Older Americans Resources and Services procedures*. Psychology Press; 2013.
49. Fillenbaum GG, Smyer MA. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. *J Gerontol*. 1981;36(4):428-434. https://doi.org/10.1093/geronj/36.4.428
50. Statistics Canada. *Canadian Community Health Survey, 2007-2008*. Abacus Data Network, V1; 2009. Available from: https://hdl.handle.net/11272.1/AB2/UITY8E
51. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of. *Am J Prev Med*. 1994;10:77-84. https://doi.org/10.1016/S0749-3797(18)30622-6
52. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. 1993;46:153-162. https://doi.org/10.1016/0895-4356(93)90053-4
53. New England Research Institutes. *PASE: Physical Activity Scale for the Elderly: administration and scoring instruction manual*. 1991. Available from: https://meetinstrumentenzorg.nl/wp-content/uploads/instrumenten/PASE-handl.pdf
54. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2024.
55. van Allen ZM, Boisgontier MP. Depressive symptoms and physical activity mediate the effect of pain on ADL and IADL functional independence in adults with arthritis: R script. *Zenodo*. 2025. https://doi.org/10.5281/zenodo.14847424
56. Hayes AF. Process: a versatile computational tool for observed variable mediation, moderation, and conditional process modeling [White paper]. 2012. http://www.afhayes.com/public/process2012.pdf

57. Robinson D, Hayes A, Couch S. broom: convert statistical objects into tidy tibbles. Version 1.0.7. CRAN; 2024. Accessed February 2, 2025. Available from: https://doi.org/10.32614/CRAN.package.broom
58. Allen L, O'Connell A, Kiermer V. How can we ensure visibility and diversity in research contributions? How the contributor role taxonomy (CRediT) is helping the shift from authorship to contributorship. *Learn Publ*. 2019;32(1):71-74. https://doi.org/10.1002/leap.1210
59. Boisgontier MP. Research integrity requires to be aware of good and questionable research practices. *Eur Rehabil J*. 2022;2(1):1-3. https://doi.org/10.52057/erj.v2i1.24