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The Relationship between Polypharmacy and Physical Activity in Those with Knee Osteoarthritis

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Abstract

Background/Objectives—Physical activity is associated with improved pain, functional status, and less disability in persons with knee osteoarthritis (OA). Since polypharmacy is related to several adverse health outcomes in older persons, we hypothesized that it might also be associated with decreased physical activity in those with knee OA. This study evaluates the relationship between the number of prescription medications and weekly moderate-vigorous physical activity (MVPA).

Design—We used hierarchical median quantile regression analysis to examine the cross-sectional association between the number of prescription medications taken in the past 30 days and the median objectively measured moderate to vigorous physical activity (MVPA) minutes controlling for demographic and clinical variables.

Setting—Four Osteoarthritis Initiative (OAI) recruitment centers in Providence, Rhode Island; Columbus, Ohio; Baltimore, Maryland; and Pittsburgh, Pennsylvania.

Participants—Accelerometer monitoring occurred in 2127 OAI participants. Of these 1889 participants had 4 or more days of valid physical activity monitoring data complete medication/covariate data (n = 38). Data were collected at the 48-month OAI follow-up visit (2008–2010).

Measurements—The outcome was weekly minutes of MVPA measured with an accelerometer. Number/type of prescribed medications and covariate data (age, sex, race/ethnicity, BMI, presence of comorbidities, pain, depressive symptoms, and radiographic knee OA severity) were taken from the public OAI database. Polypharmacy was defined as taking ≥ 5 prescribed medications.

Results—The prevalence of polypharmacy in the study population was 28.2%. Each additional prescription medication was related to a decrease of 3.6 minutes (95% CI −4.8, −2.1) in median weekly MVPA minutes. Participants meeting the polypharmacy criterion exhibited a decrease of 12.6 minutes (95% CI −21.2, −4.7) in median weekly MVPA minutes compared to those not meeting the criterion.

Conclusion—An increased number of prescription medications and polypharmacy are cross-sectionally associated with decreased MVPA in adults with knee OA. Further study is necessary to establish the causal nature of this association.

Keywords

Polypharmacy; Physical Activity; Knee Osteoarthritis; Prescription Medications

Introduction

Osteoarthritis is the most common and disabling joint disease in adults. Knee osteoarthritis (KOA) accounts for more than 80% of the disease burden of osteoarthritis and affects at least 19% of adults over the age of 45[1]. Lower levels of physical activity by individuals with KOA have been linked to a greater risk for disability and poor physical function outcomes[2]. Studies have shown that individuals with knee OA who increase physical activity have

improved pain and functional status as well as less disability[3]. Despite the known benefits of physical activity, persons with or at risk for knee OA have been found to have low levels of physical activity[4, 5]. Less than 15% of adults with or at risk for knee OA were found to meet physical activity guidelines[4, 5]. Therefore, increasing physical activity can benefit large numbers of individuals with knee OA and represents a substantial opportunity to reduce knee OA disease burden.

In order to increase the number of individuals with knee OA who are physically active, it is important to understand possible barriers to physical activity within this population. Established risk factors related to low levels of physical activity in this population are largely unmodifiable (e.g. older age, female, African American, prior knee injuries)[6,7]. One potentially modifiable but under investigated risk factor for lower physical activity is polypharmacy, which is often defined as routinely taking five or more medications[8]. Prior studies have shown polypharmacy is related to frailty, impaired mobility, disability, and falls[9,10]. Many prescription medications are associated with adverse effects which may reduce physical activity, both directly and indirectly. For example, prescription medications commonly associated with fatigue or lightheadedness may result in an unwillingness for the patient to be physically active both due to fatigue and fear of falling due to lightheadedness. Studies that have investigated the relationship between polypharmacy and adverse outcomes largely focus on older populations or populations in nursing homes[9,10,11,12]. Few studies address polypharmacy as a factor that might impact physical activity amongst community-dwelling adults with or at risk of knee osteoarthritis.

The objective of this study was to examine the association between the number of prescription medications reportedly taken and physical activity levels amongst those with or at risk of knee osteoarthritis utilizing objective physical activity measures and prescription medication data from the Osteoarthritis Initiative (OAI). We hypothesized that the number of prescription medications is inversely associated with physical activity. Additionally, we hypothesized that polypharmacy (defined as reportedly taking 5 or more prescription medications concomitantly) will be associated with decreased physical activity.

Methods

Study Design and Sample

Participants were a subcohort of adults from the Osteoarthritis Initiative (OAI)[13]. The OAI is a multi-center, longitudinal, observational study of 4796 adults aged 49 – 79 years recruited between 2004 and 2006[13]. To be enrolled in the study, adults had to have symptomatic knee OA in at least one knee or were required to have at least one risk factor from a set of established knee OA risk factors[13].

The study population for this cross-sectional analysis was drawn from the 2127 persons in the OAI accelerometer monitoring substudy at the OAI 48-month follow-up visit (2008–2010). Participants were excluded if they had fewer than four valid days of monitoring data (n = 200) or if they were missing covariate values (n = 38). Following these exclusions, the study population consisted of 1889 participants.

Measurement of Physical Activity

Objectively measured physical activity data at the OAI 48-month follow-up were used. Physical activity was measured via the ActiGraph uniaxial accelerometer (GT1M). Participants were instructed to wear the accelerometer on a belt at the natural waistline on the right hip in line with the right axilla from the time they woke up in the morning to the time they went to bed at night for seven consecutive days except for water related activities. Participants were asked to maintain a daily log to record time spent in water related activities, which the accelerometer would be unable to capture.

Uniaxial accelerometers sample and record the number and magnitude of vertical accelerations and decelerations. Activity counts were computed as the weighted sum of accelerations measured over one-minute time frames (epoch), where weights are proportional to the magnitude of the acceleration. The data was filtered using methodology validated in adults with rheumatic disease[14,15]. Non-wear periods were defined as a minimum of 90 minutes of zero activity counts (allowing for two consecutive interrupted minutes with counts ≤100). Valid physical activity monitoring was defined as 10 or more wear hours per day[4].

Total physical activity (TPA) minutes were defined as minutes with activity counts greater than 100[1], so it included all activity from the three intensity categories (light, moderate, vigorous). Weekly physical activity minutes were summed to calculate medians for two categories of physical activity. Moderate-to-vigorous physical activity (MVPA) minutes were defined as minutes with counts greater than 2020[13]. Weekly MVPA and TPA minutes were summed separately for participants with 7 days of valid monitoring; for participants with 4, 5, or 6 valid days for monitoring, weekly MVPA and TPA minutes were estimated as 7 times the average daily MVPA or TPA minutes.

Medication Assessment

The main predictor in this study was prescription medication usage at baseline. Participants were asked to bring all prescription medications they were using in the last 30 days prior to the follow-up appointment. Medications were subsequently classified and coded using the Iowa Drug Information Service classification system in the medication inventory data[16]. The number of prescription medications each participant reported taking was tallied at this follow-up visit. Polypharmacy is commonly defined in medical literature as taking five or more medications daily[8]. Therefore, we also dichotomized medication usage by 1) those participants reportedly taking 4 medications or fewer versus 2) those reportedly taking 5 or more medications.

Covariates

Demographic and health factors that could potentially affect physical activity were identified at the OAI 48 month follow up visit. Demographic factors included age, sex, and race (white or non-white). BMI calculated from height and weight measurements was used to categorize participants as underweight or normal weight (<25 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥ 30 kg/m^2). Other health factors included the presence of comorbidities estimated by the Charlson Comorbidity Index, WOMAC pain scale score (Western Ontario and

McMaster University Osteoarthritis Index pain score), high depressive symptoms [defined as modified Center for Epidemiological Studies Depression Scale (CES-D) score ≥16], and Kellgren-Lawrence (K/L) radiographic grade (0, 1, 2, 3, or 4). Radiographic evidence of KOA presence was defined as K/L grade ≥2 in either or both knees. Average daily accelerometer wear time (minutes) was also accounted for.

Statistical Analysis

Descriptive statistics summarize participant characteristics for the overall sample and by the presence or absence of polypharmacy. We examined the cross-sectional association between weekly MVPA minutes and medication usage (number of medications as well as polypharmacy) using quantile regression controlling for social-demographics and health covariates. Quantile regression is robust to outliers and does not require assumptions regarding the underlying distribution of the outcome to obtain inference tests. Three hierarchical models were fit to predict weekly MVPA. The first model included medication usage (number of medications or polypharmacy) and wear time. The second model additionally adjusted for demographic factors (age, sex, and race) and BMI. The third model further adjusted for other examined health factors (presence of comorbidity, WOMAC pain scale score, high depressive symptoms, and K/L grade). Sensitivity analyses also examined the cross-sectional association between weekly total physical activity minutes as a function of medication usage (number of medications as well as polypharmacy) using quantile regression to fit three hierarchical models.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Table 1 describes the characteristics of the 1889 participants included in this study by the presence or absence of polypharmacy. There were 533 individuals (28.2%) that met the definition of polypharmacy. The mean age in the overall sample was 65.1 (standard deviation [SD] 9.1) with 55.5% of the participants being female and 83.9% white, non-Hispanic. Amongst those with polypharmacy, there were twice as many that exhibited high depressive symptoms, 2.5 times as many participants that reported the presence of at least 1 comorbidity, and those with polypharmacy had an unadjusted median of just 44.0 minutes of weekly MVPA compared to 99.5 minutes for those without polypharmacy. Additionally, the median number of prescription medications per participant amongst those with polypharmacy was 6.0 (IQR 5.0, 8.0) compared to 2.0 (IQR 1.0, 3.0) without polypharmacy.

Weekly Moderate-to-Vigorous Physical Activity Minutes

Table 2 shows that the number of prescription medications is negatively associated with weekly MVPA minutes in the fully adjusted model. Each additional prescription medication was related to a statistically significant decrease of 3.6 minutes (95% CI −4.8, −2.1) in median weekly MVPA minutes after adjusting for demographic and health factors. Participants with polypharmacy exhibited a significant decrease of 12.6 minutes (95% CI −21.1, −4.7) in median weekly MVPA minutes adjusted for demographic and health factors compared to participants without polypharmacy (Table 3).

Sensitivity analyses examined the relationship between total time spent in physical activity with medication usage. Although total physical activity minutes tended to decrease with greater medication usage (i.e. number of prescription medications or presence of polypharmacy) these relationships were not significant after adjusting for demographic and health factors (not shown).

Discussion

We showed that there is a significant relationship between the number of prescription medications and objectively measured moderate-vigorous physical activity in this sample of persons with or at high risk of knee OA. Controlling for demographic and health factors, each additional prescribed medication was associated with a decrease of 3.6 minutes in weekly moderate-vigorous physical activity. Additionally, persons having polypharmacy (i.e. 5 or more prescription medications) had 12.6 less MVPA minutes per week after adjusting for confounders. To our knowledge, this is the first study to show that polypharmacy is associated with decreased MVPA using objectively measured physical activity.

It has been shown that decreased physical activity in patients with KOA has been linked to a greater risk for disability and poor physical function outcomes[2]. Previous studies have shown that polypharmacy is associated with frailty, impaired mobility, disability, and falls in older populations[9,10]. This study adds to the literature by showing an association between polypharmacy and decreased MVPA among adults with or at risk for KOA compared to those without polypharmacy. Furthermore, this study showed that each additional prescribed medication resulted in further decreased MVPA minutes. The unadjusted median weekly MVPA minutes for the non-polypharmacy population was 99.5 minutes compared to only 44.0 minutes for the polypharmacy population. Current guidelines recommend that adults with/without knee OA should aim for at least 150 minutes of moderate physical activity per week[17]. Bearing in mind that the KOA population struggles to meet the 150-minute guideline, it is imperative that physicians address physical activity barriers in this population in order to improve the chances of attaining the level of physical activity that can have a positive impact on functional status. Additionally, irrespective of polypharmacy, providers should assess and encourage physical activity for all of their patients. This study provides additional support to efforts to reduce polypharmacy when appropriate.

The relationship between prescription medication usage and physical activity could be related to specific medications and their side effects. For example, statins are commonly associated with myalgias which can impact physical activity. Additional commonly used prescription medications with side-effects that can affect physical activity include anti-hypertensives, which are associated with fatigue and lightheadedness, narcotic analgesics, which are associated with drowsiness and fatigue, and antihistamines, which are also associated with drowsiness and fatigue. Taking into consideration that those with more prescription medications had less physical activity, it is possible that these specific medications are interacting and increasing side effects that have a clinical impact on physical activity. This would help explain the larger drop-off in MVPA minutes seen in those who met the criteria for polypharmacy.

Our study is the first to show that polypharmacy is associated with decreased MVPA using objectively measured physical activity. Previous studies have highlighted the relationship between polypharmacy in older people and those with multiple comorbidities using self-reported measures of physical activity. These studies have also shown that polypharmacy and physical activity have an inverse relationship[11,12]. Our study shows the prominence of polypharmacy in a population that was younger and healthier than the studies that have previously examined the relationship between polypharmacy and physical activity.

There are some limitations in this study. First, there may be potential unidentified confounders as individuals reportedly taking more medications are more likely to have medical conditions which could be associated with less physical activity. We used the Charlson Comorbidity Index to control for comorbidities, however this may not fully encompass the impact that chronic medical conditions can have on physical activity. Second, while we controlled for knee pain using the WOMAC pain score and radiographic involvement using the Kellgren-Lawrence score, we may not have adequately controlled for OA severity. Third, the lower levels of physical activity found through our analysis, while statistically significant, are modest. It is not currently known what a significant difference in physical activity means in terms of health benefits. Finally, this study is a cross-sectional analysis, and causation cannot be inferred from these observational data. Longitudinal studies evaluating the potential impact of specific medications are needed to help formulate more specific recommendations.

Conclusion

In conclusion, this study found that an increase in the number of prescription medications and polypharmacy are associated with a decrease in moderate-vigorous physical activity in adults with KOA, even accounting for demographic differences and health factors. This study is the first to use objective measures of physical activity to investigate the relationship between polypharmacy and physical activity. With this data, clinicians should be aware of the number of medications their patients are prescribed and the negative impact this can have on their patients' activity levels. These findings combined with other potential adverse health outcomes associated with polypharmacy strengthens the importance of efforts to reduce polypharmacy when appropriate. Further studies are needed to confirm these findings and to better determine their clinical significance. Additionally, a longitudinal study looking at specific medications would help clarify if there are specific medications that cause a clinically meaningful and statistically significant impact on physical activity.

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Table 1.

Characteristics of Participants in the Analytic Sample

	Overall n = 1889	Absence of Polypharmacy (<5 medications) n= 1356	Presence of Polypharmacy (>5 medications) n=533
Age Mean (SD)	65.1 (9.10)	64.0 (9.0)	68.0 (8.8)
Gender: Female, n (%)	1048 (55.5%)	715 (53.5)	323 (60.6%)
Race: White, n (%)	1584 (83.9%)	1146 (84.5%)	438 (82.2%)
BMI: Mean (SD) kg/m2	28.4 (4.8)	28.1 (4.6)	29.3 (5.3)
Depression *			
High Depressive Symptoms, n (%)	220 (11.6%)	123 (9.1%)	97 (18.2%)
WOMAC Pain Scale **	2.7 (3.4)	2.5 (3.2)	3.4 (3.8)
Charlson Comorbidity Score ***			
Presence of comorbidity, n (%)	558 (29.5%)	276 (20.4%)	282 (52.9%)
K/L Grade, n (%) ****			
0	439 (23.2%)	325 (24.0%)	114 (21.4%)
1	301 (15.9%)	224 (16.5%)	77 (14.5%)
2	588 (31.1%)	432 (31.9%)	156 (29.3%)
3	391 (20.7%)	264 (19.5%)	127 (23.8%)
4	170 (9.0%)	111 (8.2%)	59 (11.1%)
Number of Prescription Medications			
Median (IQR)	3.0 (1.0, 5.0)	2.0 (1.0, 3.0)	6.0 (5.0, 8.0)
Weekly MVPA (Min)			
Median (IQR)	78.0 (26.8, 188.0)	99.5 (37.3, 210.0)	44.0 (10.0, 116.7)
Weekly Total PA (Min)			
Median (IQR)	2054.0 (1689.0, 2455.0)	2106.5 (1756.0, 2484.)	1916.0 (1520.2, 2389.0)

SD – standard deviation; IQR – Interquartile Range

* High Depressive symptoms as defined by modified Center for Epidemiological Studies Depression Scale ≥16

** WOMAC: Western Ontario and McMaster University Osteoarthritis Index pain score modified to ask about right and left knee symptoms separately, range 0–20, worse knee reported

*** Charlson Comorbidity Index

**** K/L Grade: Kellgren and Lawrence Grade, scale ranges from 0–4 with 0 no radiographic knee OA and 4 most severe radiographic knee OA

Table 2.

Median Differences in Weekly Moderate-to-Vigorous Physical Activity Minutes per Number of Prescriptions

	Model 1	Model 2	Model 3
Characteristic	***Median difference (95% CI)***	***Median difference (95% CI)***	***Median difference (95% CI)***
Number of Prescriptions	−8.5 (−10.1, −7.0)	−4.1 (−5.8, −2.9)	−3.6 (−4.8, −2.1)
Average Daily Wear Time, hours	18.0 (14.4, 21.8)	8.9 (6.5, 12.3)	8.1 (5.7, 11.2)
Age, yrs		−4.4 (−4.9, −3.9)	−4.4 (−4.8, −3.9)
Male vs Female *		42.7 (32.3, 51.3)	44.1 (34.3, 53.5)
Non-White vs White *		−13.8 (−24.6, −7.0)	−10.2 (−22.0, 0.4)
BMI, kg/m^2			
Under/Normal Weight		Reference	Reference
Overweight		−19.7 (−29.9, −9.5)	−17.4 (−29.9, −8.4)
Obese		−43.2 (−52.1, −32.5)	−40.1 (−52.2, −29.8)
High Depressive Symptoms			−4.3 (−15.3, 5.7)
WOMAC Pain Scale			−1.4 (−2.5, −0.4)
KL Grade			
0			Reference
1			−3.4 (−13.5, 12.7)
2			4.0 (−6.8, 17.4)
3			0.9 (−9.6, 14.9)
4			−7.4 (−18.9, 8.2)
Presence of Comorbidities			−6.6 (−15.1, 1.8)

* Values for number of prescriptions represent median change of weekly moderate-to-vigorous physical activity minutes with one unit increase. Female and White were the reference groups. Depressed was classified as a CES-D score > 16. BMI = body mass index; Overweight had a BMI between 25 and 30 kg/m2; Obese had BMI values greater than 30 kg/m2; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; KL= Kellgren/Lawrence

Table 3.

Median Differences in Weekly Moderate-to-Vigorous Physical Activity Minutes between Persons with and without Polypharmacy

	Model 1	Model 2	Model 3
Characteristic	***Median difference (95% CI)***	***Median difference (95% CI)***	***Median difference (95% CI)***
Polypharmacy (>5 vs <5 medications)	−45.5 (−57.0, −37.5)	−17.2 (−26.1, −10.0)	−12.6, (−21.1, −4.7)
Average DailyWear Time, hours	18.2 (14.6, 22.1)	10.5 (7.1, 13.1)	8.2 (5.2, 11.5)
Age, yrs		−4.5 (−4.9, −4.0)	−4.5 (−4.9, −4.0)
Male		42.0 (33.5, 53.0)	45.5 (34.7, 55.2)
Non-White		−15.4 (−23.8, −5.2)	−9.1 (−20.7, 2.9)
BMI, kg/m^2			
Under/Normal Weight		Reference	Reference
Overweight		−20.3 (−32.4, −10.2)	−18.7 (−29.4, −7.7)
Obese		−46.6 (−55.7, −37.3)	−43.2 (−55.3, −32.2)
High Depressive Symptoms			−6.8 (−18.1, 7.4)
WOMAC Pain Scale			−1.6 (−2.9, −0.7)
KL Grade			
0			Reference
1			−0.1 (−11.0, 14.6)
2			4.3 (−7.3, 20.0)
3			−0.3 (−9.9, 12.4)
4			−6.5 (−23.5, 7.1)
Presence of Comorbidities			−9.8 (−18.5, −0.1)

*Values for number of prescriptions represent median change of weekly moderate-to-vigorous physical activity minutes with one unit increase. Depressed was classified as a CES-D score > 16. BMI = body mass index; Overweight had a BMI between 25 and 30 kg/m2; Obese had BMI values greater than 30 kg/m2; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; KL= Kellgren/Lawrence