Phenotypes in Movement Behaviour of Patients with Hip and/or Knee Osteoarthritis – a cross-sectional study

Masterthesis

Physiotherapy Science

Program in Clinical Health Sciences

Utrecht University

Name student:	A.M.S. (Anne) de Hoop
Student number:	5911400
Date:	28-06-18

Internship supervisor(s):	Prof. Dr. C. Veenhof Dr. C.J.J. Kloek
Internship institute:	Hogeschool Utrecht, lectoraat Innovatie van Beweegzorg, Utrecht, the Netherlands
Lecturer/supervisor Utrecht University:	Dr. R. Zwitserlood

"ONDERGETEKENDE

Anne Maria Sjoerdtje de Hoop,

bevestigt hierbij dat de onderhavige verhandeling mag worden geraadpleegd en vrij mag worden gefotokopieerd. Bij het citeren moet steeds de titel en de auteur van de verhandeling worden vermeld."

Examiner

Dr. M.F. Pisters

Assessors:

Prof. Dr. C. Veenhof

Dr. J. van der Net

Masterthesis, Physical Therapy Sciences, Program in Clinical Health Sciences, Utrecht University, Utrecht, 2017

ABSTRACT

Background

Osteoarthritis is one of the most common chronic joint diseases, mostly affecting the knee or hip through pain, joint stiffness and decreased physical functioning in daily life. Regular physical activity can help preserve and improve physical functioning and reduce pain in patients with osteoarthritis. Interventions aiming to improve movement behaviour can be optimized by tailoring them to a patients' starting point; their current movement behaviour. Movement behaviour needs to be assessed in its full complexity, and therefore a multidimensional description is needed.

Objectives

The primary aim of this study was to identify phenotypes in movement behaviour of patients with hip and/or knee osteoarthritis. Second, differences between phenotypes regarding BMI, sex, age, physical functioning, comorbidities, fatigue and pain were determined.

Design and setting

In this cross-sectional study, baseline data of the clinical trial 'e-Exercise Osteoarthritis', collected in 143 Dutch primary care physical therapy practices, were analysed.

Methods

Movement behaviour was assessed with the ActiGraph GT3X and GT3X+ accelerometers. A hierarchical cluster analysis was performed in order to identify phenotypes. Second, differences between phenotypes regarding the clinical characteristics were assessed via Kruskall Wallis and Chi^2 tests.

Results

182 patients diagnosed with hip and/or knee osteoarthritis and with an average age of 63 years were included in this study. The analysis resulted in identification of four phenotypes: the continuously light active phenotype, the prolonged sedentary phenotype, the sedentary non-exercisers and the exercisers. The percentage of men was higher in the prolonged sedentary phenotype and the exercisers compared to the other phenotypes. Lower levels of pain and fatigue and higher levels of physical functioning were seen in the prolonged sedentary phenotype compared to the continuously light active phenotype and the sedentary non-exercisers. The exercisers experienced a higher level of physical functioning compared to the sedentary non-exercisers.

Conclusions

Based on multidimensional movement behaviour, four phenotypes can be identified in patients with osteoarthritis of the hip and/or knee. These have substantially different movement behaviours and clinical characteristics. Movement behaviour interventions can be improved by incorporating the knowledge about these phenotypes. Further research should test the validity of phenotypes defined here.

Keywords: osteoarthritis, physical activity, movement behaviour, phenotypes

INTRODUCTION

Osteoarthritis is one of the most common degenerative joint diseases, mostly affecting the hip and knee through pain, joint stiffness and decreased physical functioning in daily life.[1,2] Incidences of osteoarthritis are increasing and it is expected that this trend will continue in the following years. This increase has been associated with an aging population and rising obesity numbers, which are risk factors for the development of the disease.[1,3] The resulting high amount of medical visits and extensive use of medication lead to high healthcare costs on the short and longer term.[4]

Regular physical activity (PA) preserves and improves physical function and reduces pain symptoms in patients with osteoarthritis.[5,6] Conversely, spending more time in sedentary behaviour is associated with increased functional limitations.[7] Especially sedentary periods of more than 30 subsequent minutes should be avoided.[8,9] However, PA levels are often lower in this patient group compared to healthy adults.[10,11] Following recent guidelines by the World Health Organization (WHO), adults should perform moderate to vigorous PA for at least 150 minutes per week in bouts of at least ten minutes.[12] Results showed that fewer than one out of seven men and one out of twelve women with knee osteoarthritis meet these guidelines.[11] Factors associated with these lower levels of PA include older age, higher Body Mass Index (BMI), lower physical functioning and comorbidity.[13,14]

Presently, PA is often assessed with either a single measure or multiple independent measures, such as total amount of minutes spent in PA, the intensity of performed activities, or amount of active periods in a certain intensity (also called bouts) per day.[15] However, accelerometers, such as the ActiGraph GT3X, can assess PA in different dimensions simultaneously. For instance, one can assess the distribution of PA by measuring both the amount of active bouts and the total time spent in PA. Additionally, this information can be obtained for PA in different intensities and for sedentary behaviours. Only a few people score consistently across all dimensions.[16] This means that when taking only a single parameter into account, a lot of relevant information about individual movement behaviour is ignored. Therefore, the Sedentary Behaviour Research Network recently advocated a multifaceted definition of 'movement and non-movement behaviours', including all dimensions of PA, sedentary behaviour and sleep.[17] Accordingly, assessing movement behaviour in its full complexity should be preferred above single measures of PA.

Interventions for patients with osteoarthritis often aim to improve their movement behaviour by stimulating regular PA. Even though these interventions have yielded positive results, effects are small and largely inconsequential for the longer term.[18] The effectivity of these interventions can be improved by tailoring them to a patients' personal characteristics and preferences.[19] Second, often only one dimension of movement behaviour, such as increasing time spent in PA, is adressed.[20]

Understanding behaviour in its complete context is needed in order to know where best to intervene and how.[21] It can therefore be assumed that a patient's starting point, their current movement behaviour including all dimensions, can provide direction for treatment.

The heterogeneity in movement behaviours of patients with osteoarthritis can be explored by measuring multiple dimensions of PA and sedentary behaviours. With statistical methods such as the cluster analysis, phenotypes can be distinguished by grouping patients based on multiple variables simultaneously. Recent research has identified phenotypes in movement behaviours of patients with COPD and chronic cancer-related fatigue.[22,23] These phenotypes should have substantially different treatment goals.[22,23] Exploring the differences between phenotypes regarding clinical characteristics provides further insight into the needs, characteristics and common problems of specific phenotypes. This especially holds for factors that have been associated with decreased PA levels, such as physical functioning and comorbidity. Detailed, multidimensional descriptions of movement behaviour in patients with osteoarthritis of the hip and/or knee, as well as patient characteristics related to these behaviours, are lacking in current literature.

Therefore, this study aims to identify phenotypes based on movement behaviours in patients with osteoarthritis of the hip and/or knee. It is hypothesized that phenotypes can be defined based on total time and the distribution of time spent in both physical activity and sedentary behaviours. The second aim is to determine the differences between phenotypes regarding BMI, sex, age, physical functioning, comorbidities, fatigue and pain.

METHODS

Study design and setting

In this cross-sectional research, baseline data from the multicentre prospective trial 'e-Exercise Osteoarthritis'[24] were analysed. For the e-Exercise trial, 208 participants were recruited in 143 primary care physical therapy practices in three Dutch provinces. Data was collected between September 2014 and May 2015. The e-Exercise Osteoarthritis trial was approved by the Medical Ethical Committee of the St. Elisabeth hospital Tilburg, the Netherlands (Dutch Trial Register NTR4224). The current study was not reviewed by a Medical Ethical Committee since it is in the scope of the original research, as stated in the informed consents that are signed by all participants before participation.

Participants

Participants were eligible for inclusion in the trial e-Exercise Osteoarthritis if they were aged 40-80 years and if they were diagnosed with hip and/or knee osteoarthritis according to the clinical criteria of the American College of Rheumatology.[25] Excluded from the e-Exercise Osteoarthritis study were patients who (a) were on a waiting list for a hip or knee replacement surgery, (b) had a contra-indication for physical activity without supervision, determined with the Physical Activity Readiness Questionnaire (PAR-Q), (c) were sufficiently active according to the WHO health norm for PA[12], based on anamnestic information and the subjective judgement of the physical therapist, (d) participated in a physical therapy and/or physical activity program in the last six months, (e) had no access to the internet, or (f) were unable to understand the Dutch language.

Patients were included in the current study when accelerometer data from at least three consecutive days of eight hours was available. This is in accordance with guidelines for accurate measuring of physical activity from accelerometer output.[26]

Data sources

Movement behaviour was assessed with the GT3X or GT3X+ tri-axial accelerometer (ActiGraph LLC, Pensacola, FL, USA). All participants received the accelerometer with written instructions at baseline and were asked to wear the device for 5 consecutive days on an elastic belt around their waist. Exceptions were during sleep, showering and swimming. Participants were asked to document all time slots of 'wear-time' and 'non-wear time' in a diary. The device did not provide the participants with feedback regarding performed movement behaviour.

The raw output of the accelerometer provides three dimensional activity counts per minute and a vector magnitude derived from combined activity counts from the three axes. Activity counts

indicate intensity of performed activity, where higher counts stand for higher intensity. These counts are derived from the frequency and intensity of the raw acceleration and are a valid tool to calculate energy expenditure in adults.[27] Accelerometer counts and raw acceleration output of the GT3X+ are found appropriate for quantifying activity.[28] There is strong agreement between the activity counts of the GT3X and GT3X+.[29]

Raw accelerometer output was extracted and translated into clustering variables on the computer, with ActiLife software (version 5.6.1; ActiGraph LLC, Fort Walton Beach, FL, USA). Wear-time was automatically assessed, applying Troiano's (2007) definition[30]; a minimum length of 60 minutes and spike level to stop of 100 counts per minute. The resulting periods of wear-time were checked manually based on written diaries of the participants, and corrected when necessary.

Moderate to very vigorous (MV) intensity activity was defined as continuous activity of at least 2690 counts/minute[31] and sedentary behaviour was defined as continuous activity of less than 100 counts/minute.[32,33] Extracted variables (Table 1) included total minutes spent sedentary, prolonged sedentary and in MV activity per day. Also, distribution of bouts was assessed, indicated by the number of bouts per day and average length (in minutes) of bouts.

The variable total time spent in MV activity indicates the total amount of minutes per day that is spent in MV bouts of at least 10 subsequent minutes. This minimum bout length was taken in order to compare performed activity with the health norm for PA.[12] To obtain information about the distribution of all MV activity, the variables 'number of MV bouts' and 'average length of MV bouts' were obtained with a minimum bout length of 2 minutes. Total time in sedentary behaviour and total time in prolonged sedentary behaviour were extracted with minimum bout lengths of 2 minutes and 30 minutes respectively.[8,9]

Table 1.

Clustering variables

Variable name	Minimum bout length (minutes)	VM3 counts/min
Total time in MV activity per day	10	≥ 2690
Number of MV bouts per day	2	≥ 2690
Average length of MV bouts	2	≥ 2690
Total time in sedentary behaviour per day	2	<100
Total time in prolonged sedentary behaviour per day	30	<100
Number of sedentary bouts per day	2	<100

Note. MV = moderate to very vigorous; PA = physical activity; VM3 = triaxial Vector Magnitude

Physical functioning was assessed with the subscale 'function in daily living" of the Hip Osteoarthritis Outcome Score (HOOS)[34] or the Knee injury and Osteoarthritis Outcome Score (KOOS).[35] This subscale is scored on a 5-point Likert scale where 0 stands for extreme symptoms/problems and 4 stands for no symptoms/problems. The average score of all items was normalized to a score ranging from 0-100. Patients diagnosed with both hip and knee osteoarthritis filled in both questionnaires and the lowest score was taken into account.

Weight (in kg), length (in meters), age, sex and comorbidities were assessed in the baseline questionnaire. BMI was calculated as weight/length^2 and categorized in (a) <25 kg/m^2 (normal weight), (b) 25 – 29.9 kg/m^2 (overweight) and (c) >30 kg/m^2 (obese). Comorbidities were categorized to (a) none, (b) one, or (c) two or more. Pain and tiredness were assessed on a numeric rating scale, whereby 0 stood for no pain/ not tired and 10 indicated the worst possible pain/ very tired.

Statistical methods

Statistical analyses were performed in IBM SPSS Statistics for Windows (version 24, IBM Corp., Armonk, N.Y., USA). Prior to the statistical analyses, the data was checked on missing values and outliers. Correlations between clustering variables were assessed to check for multicollinearity. Variables with Pearson's correlation coefficient r>.90 were excluded from the cluster analysis.

A hierarchical cluster analysis following Ward's linkage method with Euclidean distances was performed to identify phenotypes. The number of phenotypes was based on visual inspection of the dendrogram and interpretability of the phenotypes. The identified clusters (phenotypes) were checked for normality. Because the data was not normally distributed, a non-parametric Kruskall Wallis test was performed to determine if phenotypes were significantly different on all clustering variables. In the secondary analysis, Chi^2 tests (for nominal variables) and a Kruskall Wallis test (for variables of interval and ratio level) were performed to assess the differences between the phenotypes regarding BMI, sex, age, physical functioning, comorbidities, tiredness and pain.

Sample size

There are no strict guidelines to determine the required sample size for a cluster analysis. In order to make a prediction for the minimum amount of samples, the rule-of-thumb $n \geq 2^m$, where m stands for the amount of clustering variables, is generally accepted.[36,37] For this study, this leads to a minimum sample size of $n = 2^6 = 64$.

RESULTS

Participants

182 participants were included in this study. One participant was excluded because the accelerometer data were invalid due to incorrect settings. 24 participants were excluded because less than three days of eight hours of accelerometer data were recorded. One outlier was excluded because one outcome was distanced 6.7 standard deviations from the mean, and therefore it severely influenced the clustering procedure. For the remaining 182 participants, there was no missing data.

Participant characteristics and overall outcomes on the clustering variables are shown in Table 2. The highest correlations were found for clustering variables 'Total time in prolonged sedentary bouts' versus 'Total time in MV bouts' ($r=.83$, $p<.001$) and 'Number of MV bouts' versus 'Total time in MV bouts' ($r=.63$, $p<.001$).

Identification of phenotypes

Based on visual inspection of the dendrogram and interpretation of the clusters, a choice was made for a number of clusters (phenotypes) that described the distinct movement behaviours best. This resulted in the identification of 4 phenotypes: the continuously light active phenotype, the prolonged sedentary phenotype, the sedentary non-exercisers, and the exercisers. Table 3 shows the mean scores on the clustering variables and Figure 1 shows the normalized mean values. The clustering procedure is illustrated by the dendrogram (Appendix 1). All clustering variables contributed significantly to the identification of clusters ($p<.001$).

Compared to all other phenotypes, the *continuously light active phenotype* spent the least minutes in sedentary behaviour, the least minutes in prolonged sedentary behaviour, and the least minutes in moderate to very vigorous activity. They also had the lowest number of sedentary bouts. The amount of moderate to very vigorous bouts was above average and the average duration of MV bouts was below average. Likely, this phenotype is mostly active in light intensity activities during the day.

The *prolonged sedentary phenotype* spent more minutes in sedentary bouts and prolonged sedentary bouts than all other phenotypes. The time spent in MV activity in 10 minute-bouts was with a mean of 13.0 minutes (SD=11.7) slightly above the group average. This phenotype had the highest average length of MV bouts.

The *sedentary non-exercisers* showed more breaks in sedentary behaviour compared to the prolonged sedentary phenotype, indicated by less minutes spent in sedentary and prolonged sedentary behaviour, and a higher number of sedentary bouts. The average time spent in MV bouts

of at least 10 minutes is close to zero and the number and average length of MV bouts was lower compared to all other phenotypes.

With an average daily 23.0 (SD=22.0) minutes in MV activity, the *exercisers* spent most time in MV activity of all phenotypes. This phenotype spent more time in sedentary behaviour compared to the light activities phenotype, though less than the prolonged sedentary and (moderately) sedentary non-exercising phenotype. The exercisers showed the most sedentary bouts and the least minutes in prolonged sedentary bouts, indicating the exercisers had more breaks in sedentary time.

Table 2.
Participant characteristics (N=182)

Variable	**Category**		
Age in years**,** mean (SD)	.	63.0	(8.6)
Sex, n (%)	Male	60	(33.0)
	Female	122	(67.0)
BMI, n (%)	<25 kg/m^2	59	(32.4)
	25 – 29.9 kg/m^2	76	(41.8)
	>30 kg/m^2	47	(25.8)
Location of OA, n (%)	Knee	119	(65.4)
	Hip	35	(19.2)
	Both	28	(15.4)
Time since diagnosis, n (%)	<1 year	39	(21.4)
	1 to 5 years	69	(37.9)
	>5 years	74	(40.7)
Comorbidities, n (%)	None	111	(61.0)
	Single	33	(18.1)
	Multiple	38	(20.9)
Physical functioning, mean (SD)	.	58.5	(19.7)
Fatigue, mean (SD)	.	5.1	(2.7)
Pain, mean (SD)	.	5.3	(2.3)
Accordance with health norm[a], n (%)	.	28	(15.4)
Total hours in sedentary bouts[b] **per day**, mean (SD)	.	6.2	(1.5)
Total hours in prolonged sedentary bouts[c] **per day**, mean (SD)	.	2.2	(1.4)
Total sedentary bouts[b] **per day**, mean (SD)	.	53.2	(10.0)
Total minutes in MV bouts[d] **per day**, mean (SD)	.	10.0	(14.3)
Number of MV bouts[b] **per day**, mean (SD)	.	5.3	(4.6)
Average time of MV bouts[b], mean (SD)	.	3.8	(2.0)

Note. SD = standard deviation, n = number of individuals.
[a]: Health norm for physical activity, specified as 150 minutes of MV activity per week in bouts of at least 10 minutes;[12]
[b]**:** minimum bout length: 2 subsequent minutes; [c]**:** minimum bout length: 30 subsequent minutes; [d]: minimum bout length: 10 subsequent minutes.

Table 3.

Mean scores of phenotypes on clustering variables (N=182)

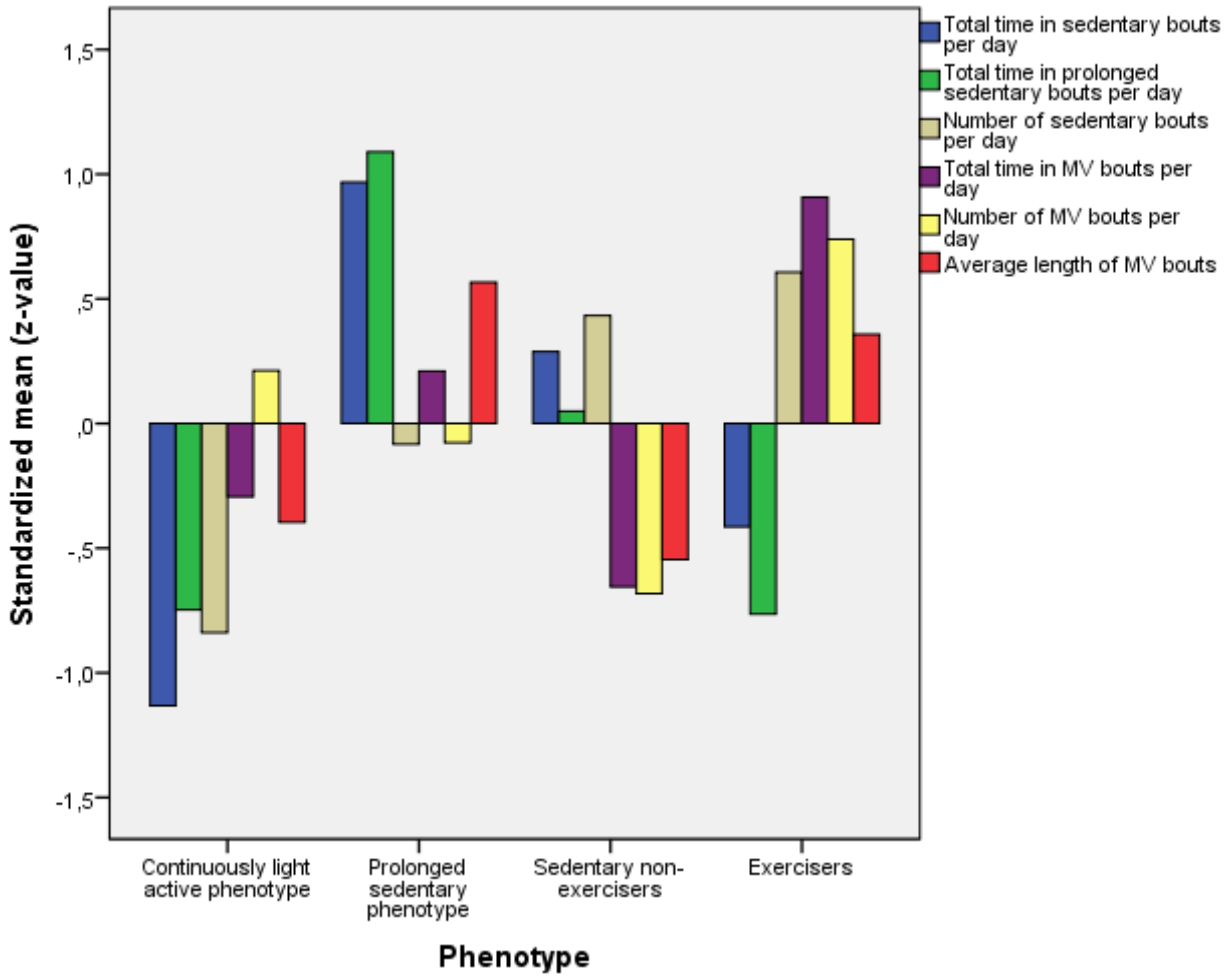
	Continuously light active phenotype	*Prolonged sedentary phenotype*	*Sedentary non-exercisers*	*Exercisers*
	n = 45	n = 54	n = 47	n = 36
Total hours in sedentary bouts[a] per day (SD)	4.5 (0.9)	7.7 (1.1)	6.7 (0.8)	5.6 (0.7)
Total hours in prolonged sedentary bouts[b] per day (SD)	1.2 (0.7)	3.7 (1.1)	2.3 (0.7)	1.1 (0.7)
Number of sedentary bouts[a] per day (SD)	44.7 (8.5)	52.3 (9.2)	57.5 (6.9)	59.3 (9.2)
Total minutes in MV bouts[c] per day (SD)	5.9 (6.1)	13.0 (11.7)	0.7 (1.5)	23.0 (22.0)
Number of MV bouts[a] per day (SD)	6.2 (3.7)	4.9 (3.5)	2.1 (1.7)	8.7 (6.5)
Average length in minutes of MV bouts[a] (SD)	3.1 (0.9)	5.0 (2.6)	2.8 (1.0)	4.5 (1.6)

Note. SD = standard deviation; n = number of individuals

[a]: minimum bout length: 2 subsequent minutes; [b]: minimum bout length: 30 subsequent minutes; [c]: minimum bout length: 10 subsequent minutes

Figure 1.

Standardized group means



Differences in clinical characteristics between phenotypes

Chi^2 tests identified a significant difference between phenotypes regarding sex. Table 4 shows that both the continuously light active phenotype and the sedentary non-exercisers consisted of fewer men compared to the prolonged sedentary phenotype (p<.001) and the exercisers (p<.001). No significant differences were found for BMI and the presence of comorbidities.

The Kruskall Wallis test did not show significant differences in age between phenotypes. Significant differences between phenotypes were identified for levels of physical functioning, pain and fatigue. Post-hoc tests with Bonferroni correction for multiple testing showed the following:

The prolonged sedentary phenotype had a higher level of physical functioning compared to the continuously light active phenotype (adjusted p<.05) and compared to the sedentary non exercisers (adj. p<.001). Second, they had lower pain levels compared to the sedentary non-exercisers (adj. p<.05) and lower pain levels compared to the continuously light active phenotype. However, the latter effect was not significant (adj. p=.08). Third, the prolonged sedentary phenotype were less fatigued compared to the continuously light active phenotype (adj. p<.05) and compared to the sedentary non-exercisers (adj. p<.05). The exercisers had significantly higher levels of physical functioning compared to the sedentary non-exercisers (adj. p<.001). Pain levels were lower compared to the sedentary non-exercisers, although this difference was not significant (adj. p=.07).

Table 4.
Differences in clinical characteristics between phenotypes

		Continuously light active phenotype	*Prolonged sedentary phenotype*	*Sedentary non-exercisers*	*Exercisers*
		n = 45	n = 54	n = 47	n = 36
Age, mean (SD)		60.9 (8.3)	65.1 (8.2)	63.4 (8.7)	62.1 (8.9)
Physical functioning, mean (SD)		53.6 (2.7)[a]	67.0 (2.3)	50.9 (3.0)[a]	61.8 (3.1)[b]
Pain, mean (SD)		5.8 (0.3)	4.7 (0.3)	6.0 (0.3)[a]	4.8 (0.4)
Fatigue, mean (SD)		5.7 (0.4)[a]	4.1 (0.4)	5.8 (0.4)[a]	4.9 (0.4)
Sex, n (%)	Male	6 (13.3)[c]	30 (55.6)[b]	6 (12.8)[c]	18 (50)[b]
	Female	39 (86.7)	24 (44,4)	41 (87.2)	18 (50)
BMI category, n (%)	<25 kg/m^2	11 (46.7)	18 (33.3)	6 (12.8)	14 (38.9)
	25 – 29.9 kg/m^2	13 (28.9)	22 (40.7)	27 (57.4)	14 (38.9)
	>30 kg/m^2	11 (24.4)	14 (25.9)	14 (29.8)	8 (22.2)
Comorbidities, n (%)	None	27 (60.0)	33 (61.1)	29 (61.7)	22 (61.1)
	Single	6 (13.3)	8 (14.8)	12 (25.5)	7 (19.4)
	Multiple	12 (26.7)	13 (24.1)	6 (12.8)	7 (19.4)

Note. SD = standard deviation; n = number of individuals.

[a]: significant difference *vs.* prolonged sedentary phenotype (p < .05); [b]: significant difference *vs.* sedentary non-exercisers (p < .001); [c]: significant difference *vs.* prolonged sedentary phenotype (p < .001)

DISCUSSION

The aim of this study was to identify phenotypes in movement behaviours of patients with osteoarthritis of the hip and/or knee. The analysis resulted in the distinction of four phenotypes: the continuously light active phenotype, the prolonged sedentary phenotype, the sedentary non-exercisers and the exercisers. Second, differences between phenotypes regarding sex, physical functioning, pain and fatigue were found.

This study highlights the heterogeneity in movement behaviours of patients with hip and/or knee osteoarthritis, resulting in the distinction of phenotypes with substantially different movement behaviours and different clinical characteristics. It also confirms that high measures of sedentary behaviour and MV activity are not mutually exclusive.[22] For example, the prolonged sedentary phenotype and the sedentary non-exercisers both spent relatively many hours in sedentary behaviour. However, while the first spent more minutes in MV activity, their daily time spent in sedentary and prolonged sedentary behaviour was substantially longer. Both being active in MV activity and limiting sedentary time are recommended for a healthy lifestyle.[8,9,12] Multidimensional measures provide a complete insight in these behaviours and can identify possibilities for individual improvements.

Interventions aiming at the improvement of movement behaviours should target different dimensions simultaneously in order to yield the best results.[16] It can also be expected that different phenotypes will benefit from different recommendations.[22,23] For instance, both the prolonged sedentary phenotype and the sedentary non-exercisers, should aim at decreasing sedentary time. While the latter could also focus on increasing time in MV activity, the prolonged sedentary phenotype could primarily aim at reducing prolonged sedentary time. Given their relatively large number of 2 minute-MV bouts and little time spent in 10 minute-MV bouts, the continuously light active phenotype could be advised to increase their average time of MV bouts in order to increase PA levels. Goals for the exercisers could be to maintain high levels of MV activity, while decreasing (prolonged) sedentary time. By integrating knowledge about characteristics of the phenotypes, future research can optimize movement behaviour interventions.

The secondary analyses highlighted clinically relevant differences between phenotypes. First, men were predominantly represented in the prolonged sedentary phenotype and the exercisers. Interestingly, these two phenotypes both spent more time in MV activity compared to the other phenotypes while their sedentary behaviours were dissimilar. This confirms an earlier assumption stating men may be more likely to participate in MV activity compared to women,[11] which could indicate that women need more or different encouragement to engage in MV activities. Second, the continuously light active phenotype and the sedentary non-exercisers both showed higher levels of

pain and fatigue and lower physical functioning compared to the other phenotypes. Coping strategies have been recommended as a moderator of how people engage in PA.[38] Presumably, patients with severe symptoms could benefit most from these strategies. Clinical practitioners should also consider the effects of common symptoms on how treatment is perceived and on how behaviours will continue after treatment.

To our knowledge, this is the first study that has identified phenotypes in movement behaviours of patients with hip and/or knee osteoarthritis. Phenotypes in movement behaviours have recently been defined in patients with COPD[22] and patients with chronic cancer-related fatigue[23]. Similar to both of these studies, we identified one most sedentary phenotype and one phenotype most active in MV activity, whereby the latter represents the smallest group. However, where Wolvers et al. found one 'average' phenotype,[23] we identified two phenotypes with mixed characteristics, i.e. the sedentary non-exercisers and the continuously light active phenotype. In both the two earlier studies, spending more time in sedentary behaviours seemed to coincide with less time in MV activity.[22,23] Unlike these findings, time spent in sedentary behaviour and MV activity appeared more independent in the current study. Lastly, this study also identified differences based on the distribution of (in)activity over the day, which increased insight in possible improvements in movement behaviour.

Obviously, different phenotypes and differences in the distribution of phenotypes may exist between patient populations. Primarily because of differences in patient characteristics which influence movement behaviour. Another factor to consider is the variability between studies in cut-off points for activity intensities and various outcome measures for movement behaviour.[17,39] It is known that appropriate cut-off points may differ between accelerometers and between populations, while these cut-off points affect measures of movement behaviours.[39] In an effort to unify existing terminologies, the Sedentary Behaviour Research Network recently proposed comprehensive definitions for all dimensions of movement behaviour.[17] More research is needed to define consistent measures for movement behaviour and to reach consensus about the right cut-off point for activity intensities. Together this will lead to better comparability between studies.

Some limitations of this study should be considered. First, participants were aware that their movement behaviour was measured and this might have led to an overestimation of performed PA. In an effort to reduce this bias, accelerometers that did not show information were used. Second, because the GT3X and GT3X+ are not water resistant, time spent for example swimming could not be recorded. For the 19 participants who reported swimming activities, measured activity was therefore underestimated. Also, based on best available literature, a subjective choice was made for the cut-off points for sedentary behaviour and MV activity.[31] The exact numbers that result from these cut-

points are suitable to compare the identified phenotypes, though comparisons with studies using different cut-points should be made with caution.

Finally, large variances in movement behaviour measures are often seen in patients with hip and knee osteoarthritis.[11,23] Large standard deviations were indeed observed for the clustering variables in all phenotypes, which challenges formulation of precise descriptions of phenotypes. Furthermore, boundaries between phenotypes may expected to be fluid in common practice. It is therefore recommended for clinical practitioners to use the phenotypes for the direction of treatment, while always accounting for an individuals' context and preferences. Further research in this patient population should test the validity of the phenotypes defined here.

CONCLUSION

Based on movement behaviours, four phenotypes can be identified in patients with hip and/or knee osteoarthritis. Besides substantial differences in movement behaviours, differences between these phenotypes exist regarding sex, physical functioning, pain and fatigue. Treatment for patients with osteoarthritis of the hip and/or knee can be personalized and optimized by incorporating this knowledge in movement behaviour interventions.

OTHER INFORMATION

Funding: There was no funding involved in this study.
Conflict of interest: None declared

REFERENCES

1. Ministerie van Volksgezondheid Welzijn en Sport. Artrose, Cijfers & Context. Available at: https://www.volksgezondheidenzorg.info/onderwerp/artrose/cijfers-context/huidige-situatie#bron--node-huisartsenregistratie-van-artrose. (Accessed: 16th March 2017)

2. Sharma, L. *et al.* Physical Functioning over Three Years in Knee Osteoarthritis: Role of Psychosocial, Local Mechanical, and Neuromuscular Factors. *Arthritis Rheum.* 48, 3359–3370 (2003).

3. Zhang, W. *et al.* OARSI recommendations for the management of hip and knee osteoarthritis. Part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthr. Cartil.* 18, 476–499 (2010).

4. National Collaborating Centre For Chronic Conditions (UK). *Osteoarthritis: National Clinical Guideline for Care and Management in Adults*. (2008).

5. Esser, S. & Bailey, A. Effects of exercise and physical activity on knee osteoarthritis. *Curr. Pain Headache Rep.* 15, 423–430 (2011).

6. Dunlop, D. D., Song, J., Semanik, P. A., Sharma, L. & Chang, R. W. Physical activity levels and functional performance in osteoarthritis initiative: a graded relationship. *Arthritis Rheumatol.* 63, 127–136 (2011).

7. Lee, J. *et al.* Sedentary behavior and physical function: Objective Evidence from the Osteoarthritis Initiative. *Arthritis Care Res. (Hoboken).* 67, 366–373 (2016).

8. Healy, G. N. *et al.* Breaks in sedentary time: Beneficial associations with metabolic risk. *Diabetis Care* 31, 661–6 (2008).

9. Ryan, C. G., Dall, P. M., Granat, M. H. & Grant, P. M. Sitting patterns at work: objective measurement of adherence to current recommendations. *Ergonomics* 54, 531–538 (2011).

10. de Groot, I. B., Bussmann, J. B., Stam, H. J. & Verhaar, J. A. N. Actual everyday physical activity in patients with end-stage hip or knee osteoarthritis compared with healthy controls. *Osteoarthr. Cartil.* 16, 436–442 (2008).

11. Dunlop, D. D. *et al.* Objective physical activity measurement in the osteoarthritis initiative: Are guidelines being met? *Arthritis Rheum.* 63, 3372–3382 (2011).

12. World Health Organization. Global Strategy on Diet, Physical Activity and Health. (2017). Available at: http://www.who.int/dietphysicalactivity/factsheet_adults/en/.

13. Veenhof, C., Huisman, P. A., Barten, J. A., Takken, T. & Pisters, M. F. Factors associated with physical activity in patients with osteoarthritis of the hip or knee: A systematic review. *Osteoarthr. Cartil.* 20, 6–12 (2012).

14. Stubbs, B., Hurley, M. & Smith, T. What are the factors that influence physical activity participation in adults with knee and hip osteoarthritis? A systematic review of physical

activity correlates. *Clin. Rehabil.* 29, 80–94 (2015).

15. Taraldsen, K., Chastin, S. F. M., Riphagen, I. I., Vereijken, B. & Helbostad, J. L. Physical activity monitoring by use of accelerometer-based body-worn sensors in older adults: A systematic literature review of current knowledge and applications. *Maturitas* 71, 13–19 (2012).

16. Thompson, D., Peacock, O., Western, M. & Batterham, A. M. Multidimensional physical activity: An opportunity, not a problem. *Exerc. Sport Sci. Rev.* 43, 67–74 (2015).

17. Tremblay, M. S. *et al.* Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project process and outcome. *Int. J. Behav. Nutr. Phys. Act.* 14, 1–17 (2017).

18. Williamson, W. *et al.* Behavioural physical activity interventions in participants with lower-limb osteoarthritis: a systematic review with meta-analysis. *BMJ Open* 5, e007642 (2015).

19. Redekop, W. K. & Mladsi, D. The Faces of Personalized Medicine: A Framework for Understanding Its Meaning and Scope. *Value Heal.* 16, S4–S9 (2013).

20. Fernandopulle, S., Perry, M., Manlapaz, D. & Jayakaran, P. Effect of Land-Based Generic Physical Activity Interventions on Pain, Physical Function, and Physical Performance in Hip and Knee Osteoarthritis. *Am. J. Phys. Med. Rehabil.* 00, (2017).

21. Davis, R., Campbell, R., Hildon, Z., Hobbs, L. & Michie, S. Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review. *Health Psychol. Rev.* 9, 323–344 (2015).

22. Mesquita, R. *et al.* Physical activity patterns and clusters in 1001 patients with COPD. 14, 256–269 (2017).

23. Wolvers, M. D. J. *et al.* Physical Behavior Profiles in Chronic Cancer-Related Fatigue. *Int. J. Behav. Med.* 25, 30–37 (2018).

24. Kloek, C. J. J. *et al.* Effectiveness and cost-effectiveness of a blended exercise intervention for patients with hip and/or knee osteoarthritis: study protocol of a randomized controlled trial. *BMC Musculoskelet. Disord.* 15, 269 (2014).

25. Altman, R. *et al.* Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheumatol.* 29, 1039–1049 (1986).

26. Hart, T. L., Swartz, A. M., Cashin, S. E. & Strath, S. J. How many days of monitoring predict physical activity and sedentary behaviour in older adults? *Int. J. Behav. Nutr. Phys. Act.* 8, 62 (2011).

27. McMinn, D., Acharya, R., Rowe, D. a, Gray, S. R. & Allan, J. L. Measuring Activity Energy Expenditure: Accuracy of the GT3X+ and Actiheart Monitors. *Int. J. Exerc. Sci.* 6, 217–229 (2013).

28. Rowlands, a. V. & Stiles, V. H. Accelerometer counts and raw acceleration output in relation to mechanical loading. *J. Biomech.* 45, 448–454 (2012).

29. Robusto, K. M. & Trost, S. G. Comparison of three generations of ActiGraph activity monitors in children and adolescents. *J. Sports Sci.* 30, 1429–1435 (2012).

30. Troiano, R. P. Large-scale applications of accelerometers: new frontiers and new questions. *Med. Sci. Sport. Exerc.* 39, 1501 (2007).

31. Sasaki, J. E., John, D. & Freedson, P. S. Validation and comparison of ActiGraph activity monitors. *J. Sci. Med. Sport* 14, 411–416 (2011).

32. Freedson, P. S., Melanson, E. & Sirard, J. Calibration of the Computer Science and Applications, Inc. accelerometer. *Med. Sci. Sports Exerc.* 30, 777–781 (1998).

33. Füzéki, E., Engeroff, T. & Banzer, W. Health Benefits of Light-Intensity Physical Activity: A Systematic Review of Accelerometer Data of the National Health and Nutrition Examination Survey (NHANES). *Sport. Med.* 47, 1769–1793 (2017).

34. de Groot, I. B. *et al.* Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score. *Osteoarthr. Cartil.* 15, 104–109 (2007).

35. Salavati, M., Akhbari, B., Mohammadi, F., Mazaheri, M. & Khorrami, M. Knee injury and Osteoarthritis Outcome Score (KOOS); reliability and validity in competitive athletes after anterior cruciate ligament reconstruction. *Osteoarthr. Cartil.* 19, 406–410 (2011).

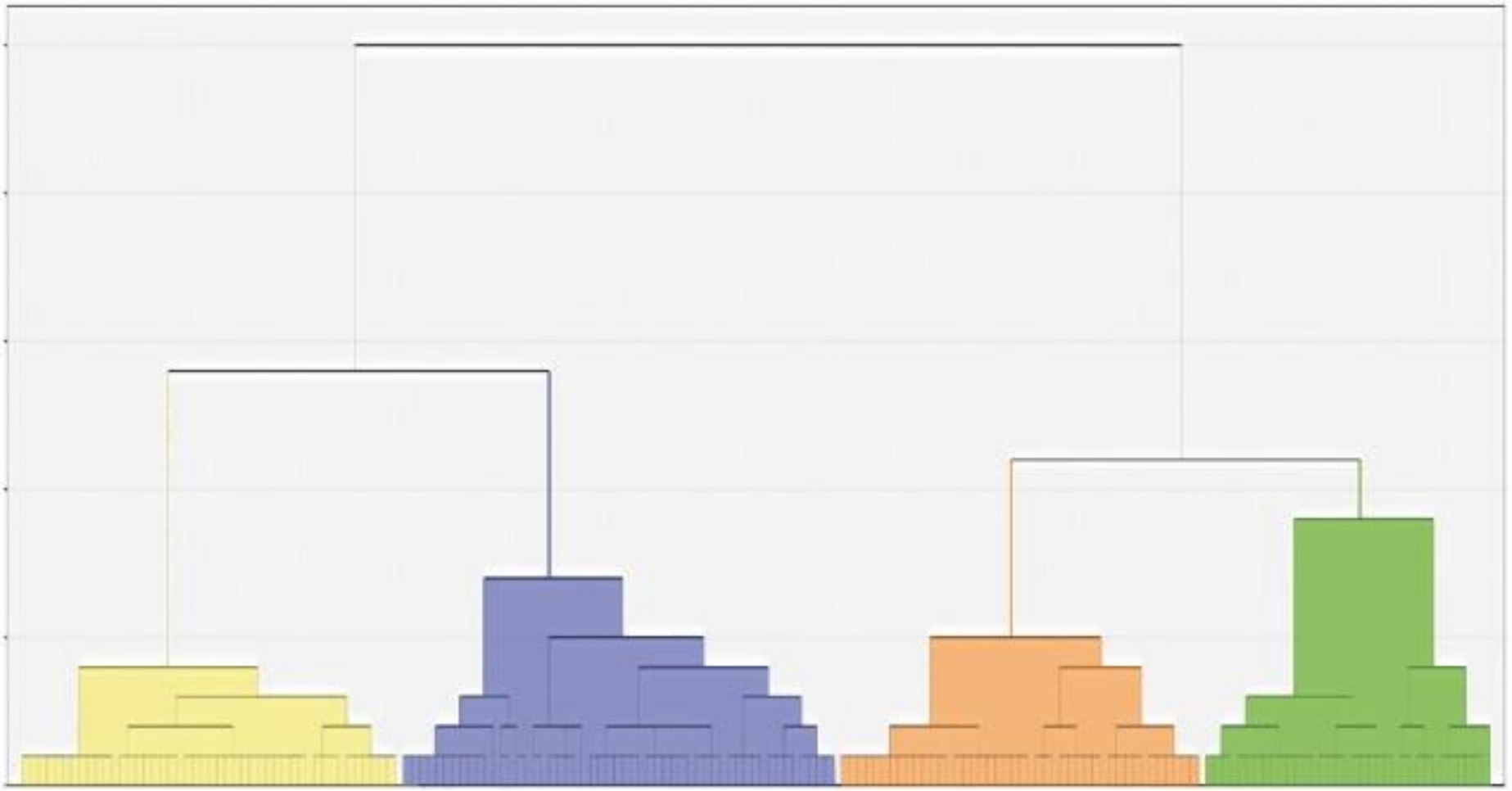
36. Dolnicar, S. A Review of Unquestioned Standards in Using Cluster Analysis for Data-Driven Market Segmentation. (2002).

37. Formann, A. K. Latent class analysis. *Encycl. Stat. Sci.* (1984).

38. Murphy, S. L., Kratz, A. L., Williams, D. A. & Geisser, M. E. The association between symptoms, pain coping strategies, and physical activity among people with symptomatic knee and hip osteoarthritis. *Front. Psychol.* 3, 1–12 (2012).

39. Orme, M. *et al.* Combined influence of epoch length, cut-point and bout duration on accelerometry-derived physical activity. *Int. J. Behav. Nutr. Phys. Act.* 11, 1–8 (2014).

APPENDIX 1. Dendrogram illustrating the clustering procedure



Note. Upwards, participants are clustered step by step based on similarities in clustering variables. Colours indicate the four identified clusters. From left to right: sedentary non-exercisers (yellow), prolonged sedentary phenotype (blue), continuously light active phenotype (red) and the exercisers (green).

SAMENVATTING

Doelstelling

Artrose is een van de meest voorkomende chronische gewrichtsaandoeningen, waarbij de knie en de heup het vaakst zijn aangedaan. De ziekte leidt tot pijn en verminderd fysiek functioneren in het dagelijks leven. Fysieke activiteit helpt om pijn te verminderen en om het fysiek functioneren zo goed mogelijk te behouden en te verbeteren. Interventies die zich richten op het verbeteren van fysieke activiteiten niveaus bij patiënten met artrose kunnen worden verbeterd door ze aan te passen aan het individu en zijn of haar huidige beweeggedrag. Beweeggedrag is complex en daarom is een multidimensionele beschrijving van het beweeggedrag van artrose patiënten nodig. Het primaire doel van dit onderzoek is om fenotypes te identificeren op basis van het beweeggedrag van patiënten met knie en/of heup artrose. Secundair worden de verschillen tussen de fenotypes aangaande BMI, geslacht, leeftijd, fysiek functioneren, comorbiditeiten, moeheid en pijn onderzocht.

Methode

Voor deze cross-sectionele studie werden de baseline data van de 'e-Exercise Artrose' studie geanalyseerd. Beweeggedrag is gemeten met de ActiGraph GT3X en GT3X+ accelerometers. Een hiërarchische cluster analyse is uitgevoerd om de fenotypes te identificeren. Verschillen tussen de fenotypes op basis van de klinische variabelen zijn onderzocht met Kruskall Wallis en Chi^2 toetsen.

Resultaten

In deze studie zijn 182 patiënten geïncludeerd met een diagnose knie en/of heup artrose. De gemiddelde leeftijd was 63 jaar. Vier fenotypes zijn geidentificeerd: het continue licht actieve fenotype, het langdurig sedentaire fenotype, de sedentaire niet-sporters en de sporters. Mannen waren het meest gerepresenteerd in het langdurige sedentaire fenotype en de sporters. Het langdurig sedentaire fenotype was gemiddeld minder moe en had minder pijn en beter fysiek functioneren in vergelijking met het continue licht actieve fenotype en de sedentaire niet-sporters. De sporters hadden beter fysiek functioneren in vergelijking met de sedentaire niet-sporters.

Conclusie

Op basis van beweeggedrag kunnen vier fenotypes geïdentificeerd worden in patiënten met knie en/of heup artrose. Deze fenotypes hebben substantieel verschillend beweeggedrag en verschillende klinische karakteristieken. Verder onderzoek moet de validiteit van deze fenotypes testen.

Klinische relevantie

Beweeginterventies voor patiënten met knie en/of heup artrose kunnen worden verbeterd door het integreren van de kennis over de verschillende fenotypes.