Use of pain medication before and after inpatient musculoskeletal rehabilitation: Longitudinal analysis of a nation-wide cohort

Mikhail Saltychev PhD, MD[1], Katri Laimi PhD, MD[1], Jaana Pentti BSc[2], Mika Kivimäki PhD[3,4*], Jussi Vahtera PhD, MD[2*]

AUTHORS' AFFILIATIONS

[1] Department of Physical and Rehabilitation Medicine, Turku University Hospital and University of Turku, Turku, Finland

[2] Department of Public Health, University of Turku and Turku University Hospital, Turku, Finland

[3] Clinicum, Faculty of Medicine, University of Helsinki, Helsinki, Finland

[4] Department of Epidemiology and Public Health, University College London Medical School, London, United Kingdom

*joint senior authors

ADDRESS FOR CORRESPONDENCE

Mikhail Saltychev, Department of Physical and Rehabilitation Medicine, Turku University Hospital and University of Turku, PO Box 52, FI-20521, Turku, Finland. E-mail: mikhail.saltychev@gmail.com, Tel.: +358 50 438 1761, Fax: +358 2 313 3730

SHORT TITLE

Pain medication before and after musculoskeletal rehabilitation

FUNDING

The Finnish Public Sector Study is supported by the EU ERA-AGE2 programme funded by the Academy of Finland (project 264944) and the participating organizations. MK is supported by NordForsk (a Nordic Research Programme on Health and Welfare) and the Finnish Work Environment Fund.

CONFLICT OF INTEREST

None to declare

ABSTRACT

Objective

To identify subgroups amongst the participants in inpatient multidisciplinary musculoskeletal rehabilitation based on the differences in the shapes of trajectories of pain medication consumption during nine years around the time of intervention.

Methods

Register-based study amongst 4 578 public sector employees. Group-based trajectory analysis of the purchase of prescribed pain medications during 9 years around the time of rehabilitation.

Results

The participants were on average 50.7 (SD 6.6) years of age, 2 955 (86%) were women. Average yearly purchase of pain medications increased during the follow-up period from 73.4 (SD 193.0) to 163.3 (SD 295.7) defined daily doses. The analysis suggested 6-cluster model. The shapes of the trajectories of three clusters did not show any steep slopes, one trajectory demonstrated nonstop rising through the entire follow-up, one trajectory was closed to the trajectory average of medication use. One trajectory (11% of the sample) demonstrated a steep growth before the intervention and steep drop after it. When comparing this cluster with all other clusters combined, ORs were 0.40 (95% CI 0.19 to 0.85) for age group (older vs. younger), 0.78 (95% CI 0.61 to 1.01) for gender (women vs. men), and 1.44 (95% CI 1.09 to 1.90) for occupational status (lower vs. higher). In other words, the participants belonged to this cluster were younger employees with a lower occupational grade.

Conclusions

It seems that younger employees in manual jobs benefit of the studied multidisciplinary musculoskeletal rehabilitation the most. Especially, when the timing of intervention is bounded to the substantial rise of pain severity.

KEYWORDS

Longitudinal analysis, rehabilitation, musculoskeletal pain, pain medication

INTRODUCTION

Multidisciplinary rehabilitation is a widely used measure to deal with disability caused by chronic musculoskeletal conditions (Kamper et al., 2015; Norlund et al., 2009; van Middelkoop et al., 2011; Waterschoot et al., 2014). While there is evidence on the effectiveness of such rehabilitation, the reports on the magnitude of the effects vary widely. These variations may be related to the content or the goal of a program, specificity of a particular musculoskeletal disorder, outcome measures, and many other known and unknown factors. Additionally to these program-specific causes of effects' variation, an intervention, even within a same training group, may have different effects on participants (Boonstra et al., 2015; Bremander et al., 2011; Kamper et al., 2015; Stigmar et al., 2013). This variation leads to an assumption that effectiveness of rehabilitation program may depend on the accuracy of participants' selection and on the timing of intervention. While being acknowledged important to maximize rehabilitation effects, the optimal timing for applying a rehabilitation intervention and predictive value of intrinsic characteristics of participants remain unrecognized. Numerous factors have been suggested as possible predictors for the outcome of rehabilitation – pain severity, number of sick leaves, gender, age, and occupational grade among others (Boonstra et al., 2015; Bremander et al., 2011; Kamper et al., 2015; Stigmar et al., 2013). Optimal timing for the rehabilitation has previously been defined for stroke or critical care patients (Laurin and Pin-Barre 2014; Wahl and Schwab 2014). One of the reason for the lack of evidence on optimal timing for chronic musculoskeletal disorders may be due to the evaluation difficulty as the best time window for participation in a program may be dissimilar for different participants even within a same training group. This within-sample heterogeneity of effect may be overlooked when considering a sample as an indivisible set. Difficulties in participants' selection process have been acknowledged by several studies (Enthoven et al., 2017; Saltychev et al., 2011)

Identifying predictors of rehabilitation outcome is a challenging task. Randomized controlled trials (the gold standard of studies on treatment effectiveness) (Fregni et al., 2010; Zlowodzki et al., 2006) can rarely be used in rehabilitation field due to both ethical issues and to impossibility to arrange a credible 'placebo' training as a control intervention. To solve this difficulty and to create a reference for intervention group, such sophisticated statistical models have been introduced as an artificial randomization by propensity score matching (Haviland et al., 2007; Saltychev et al., 2012; Streibelt et al., 2017). Another recently introduced approach, which is the main method of the present study, is to identify (within a same program or group) subgroups of persons with different responses to rehabilitation applied (Haviland et al., 2007; Howrey et al., 2017). This way, the identified subgroups can be compared to clarify some predictors of an intervention success. As far as we know, the group-based trajectory analysis (Nagin and Odgers 2010) employed in the present study has not been used by previous investigations conducted in musculoskeletal rehabilitation area. As observational longitudinal studies are common in rehabilitation research, this new technique may be of great interest for researchers. By producing statistically robust results, this approach may help clinicians and stakeholders to obtain evidence needed when justifying the use of particular of rehabilitation programs.

The main objective of the study was to identify subgroups amongst the participants in inpatient multidisciplinary musculoskeletal rehabilitation based on the differences in the shapes of trajectories of pain medication consumption during nine years around the time of intervention. The intention was to compare the characteristics of these subgroups in order to define some predictors of the rehabilitation outcome. The secondary goal was to introduce a novel statistical technique – the group-based trajectory analysis – as a plausible method of evaluating rehabilitation effects.

METHODS

Study population

This study was part of the Finnish Public Sector Study, which is an on-going prospective cohort study of employees working in 10 municipalities and 21 hospitals (REF 9). This cohort is comprised of 151 618 employees with a job contract of ≥6 months in any year between 1991 and 2005. The participants have been linked to the records of national health registers on inpatient rehabilitation and purchased prescribed pain medications, maintained by the Social Insurance Institution of Finland. The ethics committee of the Hospital District of Helsinki and Uusimaa approved the study.

Participants

From the National Rehabilitation Register kept by the Finnish Social Insurance Institution, we identified all 4 578 the cohort members who underwent inpatient musculoskeletal rehabilitation due to some chronic musculoskeletal disorder between 1996 and 2011. Age was defined in full years at the time of the rehabilitation. Occupational status was defined according to the International Standard Classification of Occupations (International Labour Organisation 2007) and then transformed into 3-class order: 1) managers, 2) other officers and 3) manual workers.

Rehabilitation

The Finnish Social Insurance Institution is one of the main providers of rehabilitation services in Finland for people of working age. It is a sponsor of several in-patient multidisciplinary rehabilitation programs arranged for people with musculoskeletal disorders. This study subjects participated in rehabilitation programs, which have been designed for people with chronic musculoskeletal disorders. The intervention represented an interdisciplinary biopsychosocial rehabilitation targeted improving or preserving health status and work ability of the working-age participants. These inpatient programs were rehabilitation courses for musculoskeletal disorders and a so-called "workplace health promotion program". These rehabilitation programs have been described in more details elsewhere (Suoyrjo et al., 2009). All the participants selected from the "workplace health promotion program" had a confirmed diagnosis of musculoskeletal disorder (M-diagnosis according to International Classification of Diseases, 10th Edition) as a main reason for rehabilitation. Although programs were implemented in different independent rehabilitation facilities, the Finnish Social Insurance Institution strictly defined the inclusion criteria, the structure of the programs, the multi-professional team composition, the modalities, and the assessment tests. The studied programs were group-based (6–10 rehabilitants per each group) containing 2–4 in-patient periods with supervised activity 4 to 6 hours per day (15–33 days in total), and the entire duration of 1–2 years. The modalities included physical training and psychological education. The participants were encouraged to adopt a healthier lifestyle, and they were expected to achieve greater aerobic capacity, muscle strength, and endurance, as well as better self-management of stress. Between the inpatient periods, the participants were expected to follow an individual exercise plan at home, which usually consisted of self-reliant physical activities and psychological exercises. The multi-professional team involved in the program consisted of a physician, a physiotherapist, a psychologist, and a vocational rehabilitation specialist. In addition, a nurse, a social worker, an occupational therapist, an occupational physiotherapist, and a nutritionist were often involved.

Potential rehabilitants were selected by their physicians. The rehabilitants had a main diagnosis of a chronic musculoskeletal disorder that had already reduced their work ability measured by elevated rate of sickness absence. Applications for rehabilitation were approved by the local offices of the Finnish Social Insurance Institution based on the physician's referral containing appropriate confirmed diagnoses.

Annual purchase of prescribed pain medication

Data on prescribed pain medication purchase were obtained from the Drug Prescription Register kept by the Finnish Social Insurance Institution. This register includes all out-patient data of filled prescriptions classified according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification code (WHO Collaborating Centre for Drug Statistics Methodology 2017) from 1994 onwards. The Drug Prescription Register does not include diagnoses for prescriptions, but the data contain the exact dates of all purchases of prescribed medications and the corresponding number of defined daily doses (DDDs). The dates and DDDs of all purchases of prescribed analgesics (ATC code N02, M01A), antidepressants (N06A), anxiolytics (N05B), hypnotics and sedatives (N05C), and muscle relaxants (M03BX02, M03BC01, M03BC51) in between Jan 1, 1994 and Dec 31, 2011 were linked to the rehabilitants. The purchase of antiepileptic drugs (N03AX) was not included in the study as they have been used for the treatment of chronic pain only for a few recent years and there were no data available on their purchase before 2003. Anti-inflammatory drugs specifically for treating rheumatoid arthritis, "osteoarthritis drugs" (e.g. glucosamine), transdermal pain medications, drugs used for treating psychosis and depression other than tricyclic antidepressants, and carbamazepine were excluded. Using 'average daily dose' as a unit, we applied a refill-sequence model to quantify the total duration of the sequence of all refills of pain medication treatment, using 100 DDDs as a maximum for a refill. The annual mean of prescribed pain medication consumption of each type of prescribed pain medications measured in DDDs was counted for the rehabilitants over the 9-year observation window covering up to 4 years before the year of rehabilitation and 4 years after that year.

Statistical analysis

Group-based trajectory modeling was used to investigate the developmental trajectory (a course of outcome over time) of the pain medication used before and after the rehabilitation. This method is a form of finite mixture modeling for analyzing longitudinal repeated measures data (Jones and Nagin 2007;

Jones et al., 2001). While conventional statistics show a trajectory of average change of outcome over time, group-based trajectory modeling is able to distinguish and describe subpopulations (clusters) existing within a studied population. The trajectories of such subpopulations may differ substantially from each other and from the average trajectory of the entire population. In this study, the procedure consisted of the following steps:

1. The values of purchased pain medications were skewed due to the overrepresentation of zeroes. Therefore, the values were converted into their normal logarithms (adding 1 in order to avoid zero values). Further trajectory analysis was conducted on that lognormal distribution.
2. Censored (known also as 'regular') normal modeling was used with minimum and maximum values set just below the lowest and, respectively, just above the highest values that occurred in the data.
3. The number of subpopulations (clusters) was defined by running the procedure several times with a number of subpopulations starting from two, and choosing the model that demonstrated significant results in at least one regression (linear, quadratic, cubic, etc.) while remaining logically plausible. While there is no absolute recommendations concerning the size of the smallest cluster, the size >5% of the sample is usually suggested (Librero et al., 2016; Nagin and Tremblay 1999). In this study, in order to limit the number of clusters to a logically acceptable level, a cut-off for the number of participants in a cluster was restricted to $\geq$10% of the sample.
4. The Bayesian Information Criterion (BIC) was used as a criterion to confirm the choice of the quantity of subpopulations considering the lesser BIC (the closest to zero) appointed to a better model.
5. The second order of multinomial logistic regression (quadratic regression) was used due to the objective of the study – to evaluate the effect of an intervention on the shape of curve. The highest order was set at the quadratic level based on the assumption that the amount of pain medication might change substantially only once (if at all) during the follow-up – at the time around the rehabilitation.
6. The participants' age, gender, and occupational grade were included into model as predictors. The cluster with the largest number of the patients served as the reference category when calculating odds ratios (OR) and 95% confidence intervals (CI).
7. To ensure that a proposed model described the real data reliably, posterior probabilities for assignment to subpopulations were calculated. In other words, we tested the degree of probability that an individual patient – in this real studied population – is assigned to one of the subgroups when using the theoretical model proposed.

8. The baseline characteristics of the subpopulations were compared using the Chi square test for ordinal variables (gender and occupational status) and the Kruskal-Wallis test for a continuous variable (age).

Age was reported as the mean and standard deviation. Occupational status and gender were reported as percentages. All the p-values were reported as 2-tailed values with the level of significance considered to be ≤ 0.05. All the analyses were carried out using Stata/IC Statistical Software: Release 14. College Station (StataCorp LP, TX, USA). The additional Stata module ‘traj’ was required to conduct group-based trajectory analysis. The module is freely available for both SAS® and Stata software (Jones and Nagin 1999; 2013).

RESULTS

The 4 578 participants were on average 50.7 (SD 6.6, range 21 to 71) years of age at the time of the beginning of rehabilitation (Table 1). Of them, 623 (14%) were men and 2955 (86%) were women. Most of the participants belonged to an age group between 40 and 60 years. Of the participants, 741 (16%) were managers, 2 434 (53%) officers, and 1 394 (31%) were employed in manual jobs. There was no loss-to-follow-up, as the data were obtained from a comprehensive national register. On average, the purchase of pain medications increased during the 9-year observation period from 73.4 (SD 193.0, range 0 to 4475) DDDs/year to 163.3 (SD 295.7, range 0 to 3630) DDDs/year. Figure 1 shows that average yearly amount of purchased pain medication was mounting through the entire 4-year period before the rehabilitation. While there was a slight decline after the rehabilitation, the quantity of pain medications remained considerably higher during four years after the intervention.

For different numbers of possible subpopulations (from two to six), BIC estimates varied slightly: -73356.6 for 2-cluster model, -72194.6 for 3-cluster, -71683.5 for 4-cluster, -71440.2 for 5-cluster, and -71112.9 for 6-cluster model. This way, a 6-cluster model demonstrated the smallest BIC and it was acceptable based on the size of the smallest cluster (11%) as well. Thus, further analyses were conducted using these six clusters (named here from '1' to '6' for convenience).

The characteristics of the six clusters are presented in Table 1. There were statistically significant differences in frequencies of every risk factor between the clusters. The suggested model was robust with high average posterior probabilities for all three clusters from 0.77 to 0.92 (Table 2). The odds of correct classification ranged from 15 to 44.

The shapes of the trajectories of clusters 1, 5, and 6 were alike even if the exact masses of purchased medications were different. They did not show any steep slopes and overall were close to a linear relationship. The trajectory of cluster 2 demonstrated nonstop rising through the entire follow-up. The shape of cluster 3 trajectory resembled the shape of the average trajectory seen in Figure 1. The most attention-grabbing trajectory profile was seen in the cluster 4 (representing the 11% of the sample) – the amount of purchased medications grew previously to the intervention and then dropped down approaching zero level at the end of follow-up. Based on the results, 90% of the participants did not benefit of the intervention when outcome was indirectly measured by the change in pain severity (Figure 2).

In the analysis of risk factors, the cluster 6 was used as a reference as the largest cluster of six identified ones (Table 3). Based on Figure 2, the most attention was drawn to the cluster 4. As predicted by the model, the effect of age was insignificant. Instead, female gender (OR 0.64, 95% CI 0.45 to 0.89) decreased and lower occupational status (OR 1.31, 95% CI 1.08 to 1.58) increased the probability to be included into this cluster. When comparing the cluster 4 with all other clusters combined, ORs were 0.40 (95% CI 0.19

to 0.85) for age group (older vs. younger) and 1.44 (95% CI 1.09 to 1.90) for occupational status (lower vs. higher). In other words, the participants belonged to this cluster were younger employees with a lower occupational grade.

DISCUSSION

This longitudinal register-based nation-wide cohort study evaluated the trajectories of pain medication purchases made by 4 578 participants in musculoskeletal multidisciplinary inpatient rehabilitation programs. The use of pain medication was analyzed in a time window of 9 years around the intervention. Of the participants, 75% purchased as much pain medication before the intervention as after it or increasingly raised their consumption of pain medication despite the intervention. Within the cohort participants, group-based trajectory analysis revealed six subpopulations with trajectories of different shapes. The analysis included three predictors – age, gender, and occupational status. Of these six trajectories, three approached a linear shape; one was similar to a trajectory average in the sample; and one demonstrated a continuing rising through the entire follow-up. The most interesting finding was related to the shape of the trajectory of cluster #4 (11% of the sample) in Figure 2. This trajectory demonstrated a sharp rise of pain medication use before the rehabilitation and a corresponding steep decrease (all the way down to zero) within four years after the intervention. Compared to the rest of the cohort, the persons who belonged to this cluster were younger employees with lower occupational status. It seems that only 11% have profited of the rehabilitation enough to decrease their need for pain medication.

Of the broad spectrum of possible predictors of rehabilitation outcome, only three (age, gender, and occupational status) were available from the registers for the analysis. However, it should be emphasized that the main goal of this study was identifying the existence of different trajectories within the cohort rather than explaining their differences by a very limited number of risk factors. The cohort was predominated by women and by people of middle age (from 40 to 60 years) employed in public sector. These cohort limitations may affect the generalizability of the results across other populations. Even with these weaknesses in mind, the results remain important for both practitioners and researchers in rehabilitation field. The study was based on a nation-wide population and reliable state-maintained registers without missing data for a long-time window of nine years. Even though trajectories only show the tendencies and they are not directly applicable to all individual rehabilitants, the size of the studied cohort and the long follow-up time ensure the reliability of these tendencies. Randomized controlled trials are still more uncommon in rehabilitation field than in other clinical areas (Fregni et al., 2010; Zlowodzki et al., 2006). This fact leads to a situation when confirming the effectiveness, the optimal timing, or the succeeded selection of rehabilitation participants is more difficult than in many other clinical fields. The main statistical method used here creates a rare chance to investigate the timing of rehabilitation and helps to understand better the reasons why the same rehabilitation approach may produce a different outcome among the participants.

It is self-evident that the effectiveness of multidisciplinary intervention cannot be measured solely by the purchase of prescribed pain medication. However, pain medication reflects indirectly the intensity and frequency of pain, which are essential when evaluating functioning and work-ability – the common target of musculoskeletal rehabilitation for people of working age.

The value of different factors as predictors of the success of multidisciplinary musculoskeletal rehabilitation has not been established well (Boonstra et al., 2015; Bremander et al., 2011; Saltychev et al., 2011; Stigmar et al., 2013; Wahl and Schwab 2014). It has been appointed that the outcomes of rehabilitation may strongly depend on the right timing and the appropriate selection of the participants. That conception got a support from the results of this study. It seems that younger men working in manual jobs are more prone to benefit of the rehabilitation, especially, when the timing is right – at the peak of their consumption of pain medications.

The effect of gender on the results of rehabilitation has previously been described by a few studies while the reasons for that connection remains unknown (Haukenes et al., 2015). It can only be speculated if men are more eager to start physical training during the rehabilitation than women do or if women are more physically active already before rehabilitation and cannot reach additional benefit during their rehabilitation. The effects of age and occupational status have also been previously described by only a few trials (Bremander et al., 2011). Working conditions and working positions are probably more challenging with low educational status with a need for optimal muscular functions and aerobic capacity. Thus, the negative correlation between occupational status and rehabilitation effect was unexpected. One can only assume that younger persons are more likely to follow the instructions given by a physiotherapist during the rehabilitation while the persons employed in manual jobs may possess better physical readiness to perform training exercises.

This study used a so-called ‘soft’ outcome measure – change in pain severity as indicated by the usage of pain medications. The main goal of all the studied programs was, however, maintaining the work ability of the participants. Thus, further research may reveal will these results endure when assessed by different outcomes including ‘hard’ measures like the change in the number of sick leaves. The results also need a confirmation from additional research in different cultures, settings, and specific types of musculoskeletal disorders.

Conclusions

It seems that younger employees in manual jobs benefit of the studied multidisciplinary musculoskeletal rehabilitation the most. Especially, when the timing of intervention is bounded to the substantial rise of pain severity.

Table 1. Distribution of age, gender, and occupational status within the sample.

Cluster	n	%	Age		Age group										Gender				Occupational grade					
					≤30		≤40		≤50		≤60		>60		Men		Women		Manager		Officer		Manual worker	
			Mean	SD	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1	651	14	51.3	6.0	2	0	41	6	202	32	380	60	10	2	125	19	526	81	145	22	329	51	174	27
2	492	11	51.0	6.2	3	1	28	6	161	33	281	58	12	2	67	14	425	86	77	16	274	56	141	29
3	706	15	49.9	6.8	6	1	71	10	247	35	358	51	15	2	86	12	620	88	117	17	376	53	213	30
4	495	11	51.0	7.3	9	2	40	8	142	28	297	59	16	3	83	17	412	83	70	14	240	48	185	37
5	973	21	50.6	6.7	8	1	78	8	327	33	555	56	21	2	122	13	851	87	136	14	505	52	329	34
6	1261	28	50.5	6.6	9	1	95	8	459	36	674	54	22	2	140	11	1 121	89	196	16	710	56	352	28
Total	4578	100	50.7	6.6	37	1	353	8	1 540	34	2551	56	97	2	623	14	3955	86	741	16	2434	53	1394	31

Table 2. Posterior probabilities for belonging to the identified clusters

Parameter	Clusters					
	1	2	3	4	5	6
Average posterior probabilities	0.88	0.77	0.78	0.80	0.80	0.92
Odds of correct classification	43.89	28.60	19.49	32.92	14.99	28.54
Proportion in each group based on the assignments for the maximum posterior probability	0.14	0.11	0.15	0.11	0.21	0.28
Expected number based on the sums of the posterior probabilities	0.14	0.11	0.15	0.11	0.22	0.28

Table 3. Probability of group membership depending on age group, gender, and occupational status (n=4 569)

Odds ratios (OR) and 95% confidence intervals (95% CI) derived from a multinomial logistic regression model with all parameters adjusted for each other. The reference group is the largest cluster 6 (28% of the entire sample

Cluster	Risk	Predicted by the model		
		OR	95%CI	95%CI
1	Age group [a]	1.22*	1.04	1.43
	Female vs. male	0.42*	0.32	0.57
	Occupational status [b]	0.73*	0.62	0.86
2	Age group [a]	1.16	0.97	1.38
	Female vs. male	0.85	0.57	1.26
	Occupational status [b]	1.00	0.83	1.20
3	Age group [a]	0.94	0.81	1.10
	Female vs. male	0.82	0.58	1.16
	Occupational status [b]	0.99	0.84	1.18
4	Age group [a]	1.09	0.91	1.30
	Female vs. male	0.64*	0.45	0.89
	Occupational status [b]	1.31*	1.08	1.58
5	Age group [a]	1.03	0.89	1.18
	Female vs. male	0.92	0.67	1.26
	Occupational status [b]	1.27*	1.09	1.48

[a] Descending order starting from >60 years; [b] Manual worker vs. manager or officer

Figure 1. Regression curve of the average change in amount of pain medications purchased during 9 years around the time of the beginning of rehabilitation.

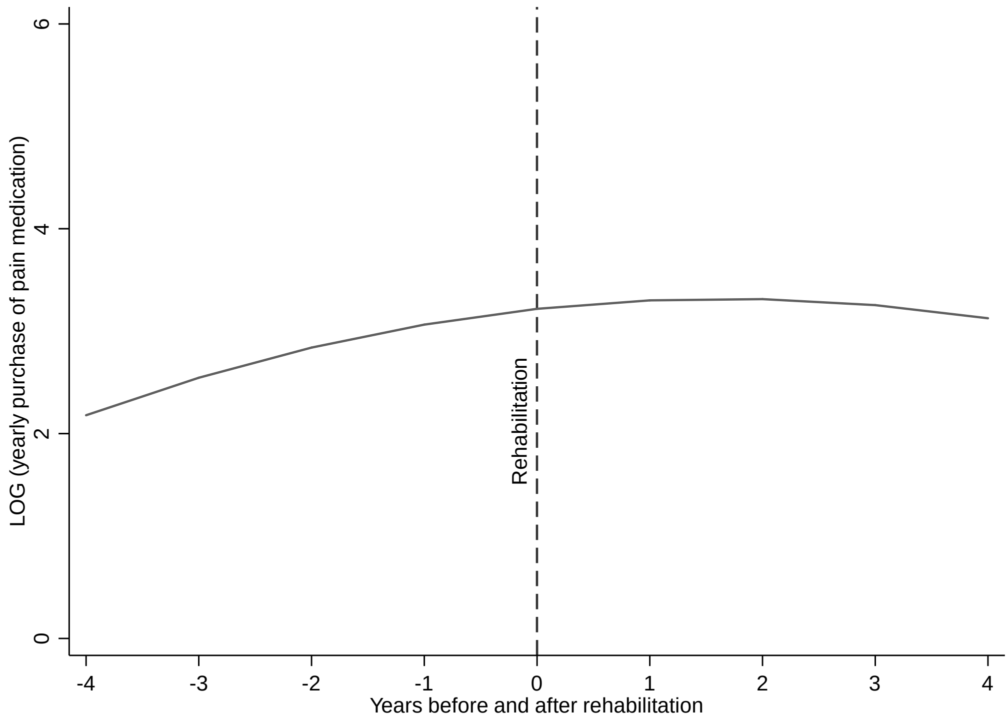
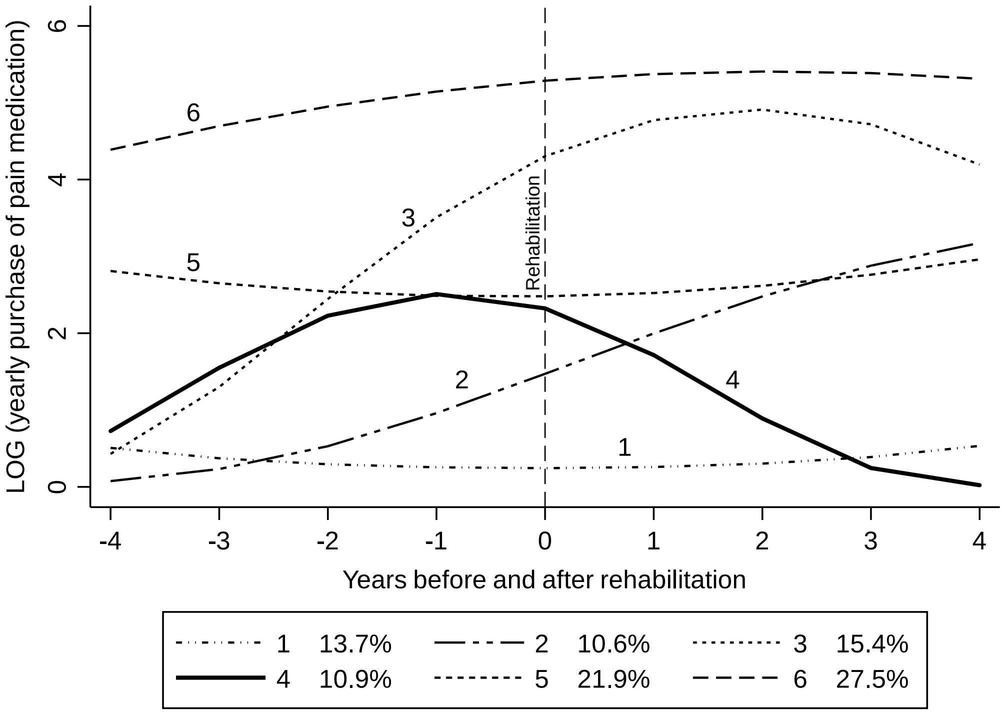


Figure 2. Group-based trajectory analysis of the amount of pain medications purchased during 9 years around the time of the beginning of rehabilitation.



REFERENCES

Boonstra AM, Reneman MF, Waaksma BR, Schiphorst Preuper HR, Stewart RE. Predictors of multidisciplinary treatment outcome in patients with chronic musculoskeletal pain. Disabil Rehabil 2015;37: 1242-1250.

Bremander AB, Holmstrom G, Bergman S. Depression and age as predictors of patient-reported outcome in a multidisciplinary rehabilitation programme for chronic musculoskeletal pain. Musculoskeletal Care 2011;9: 41-48.

Enthoven P, Molander P, Oberg B, Stalnacke BM, Stenberg G, Gerdle B. Do pain characteristics guide selection for multimodal pain rehabilitation? J Rehabil Med 2017;49: 161-169.

Fregni F, Imamura M, Chien HF, Lew HL, Boggio P, Kaptchuk TJ, Riberto M, Hsing WT, Battistella LR, Furlan A, International placebo symposium working g. Challenges and recommendations for placebo controls in randomized trials in physical and rehabilitation medicine: a report of the international placebo symposium working group. Am J Phys Med Rehabil 2010;89: 160-172.

Haukenes I, Hensing G, Stalnacke BM, Hammarstrom A. Does pain severity guide selection to multimodal pain rehabilitation across gender? Eur J Pain 2015;19: 826-833.

Haviland A, Nagin DS, Rosenbaum PR. Combining propensity score matching and group-based trajectory analysis in an observational study. Psychol Methods 2007;12: 247-267.

Howrey BT, Graham JE, Pappadis MR, Granger CV, Ottenbacher KJ. Trajectories of functional recovery following inpatient rehabilitation for traumatic brain injury. Arch Phys Med Rehabil 2017.

International Labour Organisation. International Standard Classification of Occupations. 2007; Available from: www.ilo.org/public/english/bureau/stat/isco/.

Jones BL and Nagin DS. traj - group-based modeling of longitudinal data. 1999; Available from: www.andrew.cmu.edu/user/bjones/.

Jones BL and Nagin DS. Advances in Group-Based Trajectory Modeling and an SAS Procedure for Estimating Them. Sociological Methods & Research 2007;35: 542-571.

Jones BL and Nagin DS. A Note on a Stata Plugin for Estimating Group-based Trajectory Models. Sociological Methods & Research 2013;42: 608-613.

Jones BL, Nagin DS, Roeder K. A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. Sociological Methods & Research 2001;29: 374-393.

Kamper SJ, Apeldoorn AT, Chiarotto A, Smeets RJ, Ostelo RW, Guzman J, van Tulder MW. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. BMJ 2015;350: h444.

Laurin J and Pin-Barre C. Physiological Adaptations Following Endurance Exercises after Stroke: Focus on the Plausible Role of High-Intensity Interval Training. Int J Phys Med Rehabil 2014;S3: 1-6.

Librero J, Sanfelix-Gimeno G, Peiro S. Medication Adherence Patterns after Hospitalization for Coronary Heart Disease. A Population-Based Study Using Electronic Records and Group-Based Trajectory Models. PLoS One 2016;11: e0161381.

Nagin D and Tremblay RE. Trajectories of boys' physical aggression, opposition, and hyperactivity on the path to physically violent and nonviolent juvenile delinquency. Child Dev 1999;70: 1181-1196.

Nagin DS and Odgers CL. Group-Based Trajectory Modeling (Nearly) Two Decades Later. J Quant Criminol 2010;26: 445-453.

Norlund A, Ropponen A, Alexanderson K. Multidisciplinary interventions: review of studies of return to work after rehabilitation for low back pain. J Rehabil Med 2009;41: 115-121.

Saltychev M, Laimi K, El-Metwally A, Oksanen T, Pentti J, Virtanen M, Kivimaki M, Vahtera J. Effectiveness of multidisciplinary primary prevention in decreasing the risk of work disability in a low-risk population. Scand J Work Environ Health 2012;38: 27-37.

Saltychev M, Laimi K, Oksanen T, Pentti J, Virtanen M, Kivimaki M, Vahtera J. Predictive factors of future participation in rehabilitation in the working population: the Finnish public sector study. J Rehabil Med 2011;43: 404-410.

Stigmar KG, Petersson IF, Joud A, Grahn BE. Promoting work ability in a structured national rehabilitation program in patients with musculoskeletal disorders: outcomes and predictors in a prospective cohort study. BMC Musculoskelet Disord 2013;14: 57.

Streibelt M, Burger W, Nieuwenhuijsen K, Bethge M. Effectiveness of Graded Return to Work After Multimodal Rehabilitation in Patients with Mental Disorders: A Propensity Score Analysis. J Occup Rehabil 2017.

Suoyrjo H, Oksanen T, Hinkka K, Pentti J, Kivimaki M, Klaukka T, Vahtera J. A comparison of two multidisciplinary inpatient rehabilitation programmes for fibromyalgia: a register linkage study on work disability. J Rehabil Med 2009;41: 66-72.

Wahl AS and Schwab ME. Finding an optimal rehabilitation paradigm after stroke: enhancing fiber growth and training of the brain at the right moment. Front Hum Neurosci 2014;8: 381.

van Middelkoop M, Rubinstein SM, Kuijpers T, Verhagen AP, Ostelo R, Koes BW, van Tulder MW. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. Eur Spine J 2011;20: 19-39.

Waterschoot FP, Dijkstra PU, Geertzen JH, Reneman MF. Dose or content? Effectiveness of pain rehabilitation programs for patients with chronic low back pain: A systematic review. Aurthor reply. Pain 2014;155: 1902-1903.

WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2017. 2017; Available from: www.whocc.no/atc_ddd_index.

Zlowodzki M, Jonsson A, Bhandari M. Common pitfalls in the conduct of clinical research. Med Princ Pract 2006;15: 1-8.