#### Open Access Full Text Article

ORIGINAL RESEARCH

Incidence of Free of Charge Physiotherapy in a Danish National Cohort of Stroke, Parkinson's Disease, Multiple Sclerosis and Rheumatoid Arthritis Patients

> This article was published in the following Dove Press journal: *Clinical Epidemiology*

Erhard Trillingsgaard Næss-Schmidt <sup>1</sup> David Høyrup Christiansen<sup>2,3</sup> Rene Drage Østgård <sup>6</sup> Nils-Bo de Vos Andersen<sup>5</sup> Jørgen Feldbæk Nielsen<sup>1</sup> Lene Odgaard <sup>6</sup>

<sup>1</sup>Hammel Neurorehabilitation Centre and University Research Clinic, Hammel, Denmark; <sup>2</sup>Occupational Medicine, Danish Ramazzini Centre, Regional Hospital West Jutland - University Research Clinic, Herning, Denmark; <sup>3</sup>Department of Clinical Medicine, Health, Aarhus University, Aarhus, Denmark; <sup>4</sup>Diagnostic Center, Silkeborg Regional Hospital, Silkeborg, Denmark; <sup>5</sup>Primary Health Care and Quality Improvement, Viborg, Denmark

Correspondence: Erhard Trillingsgaard Næss-Schmidt Hammel Neurorehabilitation Centre and University Research Clinic, Institute of Clinical Medicine, 15 Voldbyvej, Hammel 8450, Denmark Tel +45 78419062 Email erhnae@rm.dk



**Background:** Denmark is a welfare state with a publically funded healthcare system that includes the right to free of charge physiotherapy (FCP) for patients with chronic or progressive disease who fulfill strict criteria. The aim of this study was to investigate the incidence of referral to FCP in patients with a hospital diagnosis of stroke, multiple sclerosis (MS), Parkinson's disease (PD) and rheumatoid arthritis (RA) between 2007 and 2016.

**Methods:** The study was register-based and included data from The Danish National Patient Registry and The National Health Service Registry. The study population included the four largest disease groups receiving FCP in Denmark. The incidence of receiving FCP was reported as the cumulated incidence proportion (CIP).

**Results:** The study showed that FCP was mainly initiated within the first 2 years after diagnosis. The 2-year CIP was 8% for stroke patients, 53% for PD patients, 49% for MS patients, and 16% for RA patients. The proportion of patients referred to FCP generally increased over the period of the study due to more patients being referred from medical specialists in primary care.

**Conclusion:** This study found substantial differences in the incidence of referral to FCP in a Danish population of stroke, PD, MS and RA patients.

**Keywords:** non-pharmacologic treatment, chronic disease, progressive disease, rehabilitation

## Introduction

Patients with a chronic disease may need support to manage everyday activities and thus maintain a meaningful life.<sup>1</sup> Systematic reviews of chronic disease recommend different forms of exercise, to reach a higher functional level.<sup>2–5</sup> However, motivational and psychological factors can influence whether a person continues to be active and how he/she self-manages this activity.<sup>6</sup> Therefore, providing continuous support in the chronic stage of diseases may prove beneficial.

Denmark is a welfare state with a population of 5.7 million and a publicly funded health care system. This healthcare system includes the right to free of charge physiotherapy (FCP) for patients with severe physical disability or progressive disease who fulfill strict diagnostic criteria specified by the Ministry of Health. FCP is provided by private primary care clinics on a contract with the Ministry of Health. Every 4 weeks, the primary care clinics get reimbursements through the tax-financed health care

Clinical Epidemiology 2020:12 23-29

© 2020 Nass-Schmidt et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/ the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for Commercial use of this work, peaks ese paragraph 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php). system. In 2016 the FCP service included more than 67,000 patients and the economic burden was more than 850 million Danish Kroner/113 million Euro (National Health Service Registry).

The purpose of FCP is either to increase or maintain function, or to delay loss of function by providing treatment and team-based training. Patients are referred to FCP by primary care or hospital-based medical specialist. The specific criteria for receiving FCP include (i) having one of 43 FCP diagnoses defined The Danish Health Authority,<sup>7</sup> (ii) having a severe physical disability, defined as "a person who cannot manage her- or himself indoors for 24 hrs without help or aids for daily personal living", and iii) having a prognosis that the disease will last more than 5 years. In August 2008, FCP was expanded to include patients with a progressive disease, defined as "an abnormal function of the sensor-motoric system or nervous system", and patients in this group no longer needed a severe physical disability to be eligible to receive FCP.

The four largest disease groups receiving FCP are stroke, multiple sclerosis (MS), Parkinson's disease (PD) and rheumatoid arthritis (RA). These groups account for more than half of the FCP population. Until now, nothing has been published on demographics or incidence of referral in patients receiving FCP in Denmark.

Increasing elder population and the expectations of a higher incidence of chronic disease in the future motivate more knowledge on services such as FCP. The aim of this study is to investigate the incidence of referral to FCP in stroke, PD, MS and RA patients in the period from 2007 to 2016.

# **Materials and Methods**

## Data Sources

We conducted a population-based, nationwide cohort study. All data were retrieved from Danish administrative registries through Statistics Denmark.<sup>8</sup> The Danish National Patient Registry (DNPR) contains data on all hospital contacts, including ambulatory visits, and serves as a registry for hospital payments and thus considered largely complete.<sup>9</sup> The National Health Service Registry (DHSR)<sup>10</sup> contains data on primary health care services, including amount and type of FCP, and coverage is assumed to be good as it serves as a registry for reimbursements.

Data were linked across registries using the personal identification number assigned to all citizens in Denmark.<sup>11</sup> Approval for the study was given by the Central Denmark Region Data Protection Agency (ref nr. 1-16-02-757-17).

## Study Population

We obtained data from the DNPR on all residents in Denmark registered with a primary ICD10 diagnosis of stroke (DI60.0–DI60.9, DI61–DI64, DG45.0–DG45.2, DG45.8, DG45.9), PD (DG20, DG21.0–DG21.3, DG21.8–DG21.9, DG22), MS (DG35) or RA (DM05.0, DM05.9, DM06.0, DM06.9, DM12.3) from 1998 to 2016 (n=311,491). The validity of stroke, PD, MS and RA diagnoses in the DNPR has previously been reported.<sup>12–15</sup>

Patients were divided into four groups, each of them including patients diagnosed with only the specific disease of interest (Stroke, PD, MS, RA) and a fifth mixed group including the patients registered with two or more of the four diseases of interest.

Based on these data, we identified patients over a 10year period with first-time diagnoses of stroke, PD, MS or RA between 2007 and 2016 (by excluding patients registered with one of the four diagnoses of interest between 1998 and 2006 (n=134,668). Patients diagnosed with two or more of the four diseases of interest (n=2109) were also excluded. The final population therefore included 174,714 individuals with incident hospital diagnoses of stroke, PD, MS or RA from 2007 to 2016.

# Data Analysis

Data on FCP services were retrieved for all participants from the DHSR. As the FCP services are reimbursed every 4 weeks, we defined FCP after the diagnosis as FCP reimbursements >4 weeks after the date of the hospital diagnosis. FCP before the diagnosis was defined as FCP reimbursements before or up to 4 weeks after the hospital diagnosis. The proportion of individuals with FCP was calculated as the cumulated incidence proportion (CIP). Individuals were followed until the first session of FCP after the hospital diagnosis, death (competing event), or the end of follow-up (December 2016), whichever occurred first.

At time points 0.5, 1, 2, 3, 4, and 5 years the overall CIP and the CIP among those not receiving FCP before the hospital diagnosis was calculated for each of the four diagnoses. As the level of dependence and thereby the need for FCP may differ within the stroke sub-diagnoses, the CIP was additionally graphed for each sub-diagnosis of stroke.

To explore time trends in the use of FCP, the CIP was graphed separately for each calendar year of diagnosis grouped in 2-year periods. To explore whether the legislative changes in 2008 affected the access to FCP, the CIP was also graphed separately for the year 2007. All analyses were performed using STATA version 15 (StataCorp LP, College Station, Texas)

## Results

Our study included 174,714 individuals. Of these, 83% had a stroke diagnosis, 4% had a PD diagnosis, 3% had an MS diagnosis, and 9% had an RA diagnosis. One hundred twenty-seven thousand five hundred and thirty-one (73%) of these individuals were followed until their last FCP session or the end of the study period, and 47,183 (27%) died. The percentage of deceased patients within the individual diagnoses was 30% among stroke patients,

21% among PD patients, 2% among MS patients, and 10% among RA patients. FCP was provided for 26,152 individuals with stroke (56%), PD (16%), MS (14%) and RA (14%). The percentage of patients receiving FCP before the hospital diagnosis increased over the study period. Further characteristics of the individuals receiving FCP are presented in Table 1.

# The Incidence of Referral to FCP After the First Hospital Diagnosis

Patients with PD and MS were the quickest to begin FCP with 20% of PD patients and 13% of MS patients starting

**Table I** Characteristics of Patients After Incident Hospital Diagnoses of Stroke, Parkinson's Disease (PD), Multiple Sclerosis (MS) and Rheumatoid Arthritis (RA), %

	Stroke (n=14,669)	PD (n=4277)	MS (n=3533)	RA (n=3673)	
Female sex	48.3	41.3	72.1	82.1	
Age at FCP Initiation					
0–18 years	0.5	0.1	0.9	2.0	
18–39 years	2.6	0.7	37.9	12.8	
40-64 years	32.1	23.3	54.4	50.9	
≥65 years	64.8	76.0	6.8	34.3	
Civil Status at FCP Initiation					
Unmarried	12.1	7.0	33.1	18.2	
Married/civil partnership	51.8	64.6	52.7	55.7	
Divorced/dissolved	15.8	9.8	11.7	14.1	
Widowed	20.3	18.7	2.5	12.1	
Employment Status at FCP Initiation					
Employed	18.5	17.3	59.1	39.1	
Unemployed	0.4	0.3	2.3	1.1	
Not in work force:					
• < 16 years old	0.2	0.0	0.1	0.3	
• Temporary leave of absence	3.7	1.0	9.9	5.6	
• Retired <sup>a</sup>	71.3	76.4	17.5	43.2	
• Other	5.8	4.7	10.7	10.8	
Missing	0.2	0.3	0.5	0.0	
Charlson Comorbidity Index at FCP Initiation <sup>b</sup>					
0 point	61.8	78.3	93.5	86.6	
l point	17.8	11.3	3.5	7.1	
≥ 2 points	20.4	10.5	3.1	6.3	
Received FCP before hospital diagnosis, overall	14.3	45.2	27.0	33.8	
Year of diagnosis 2007–2008	11.9	32.5	20.6	29.6	
Year of diagnosis 2009–2010	12.5	37.1	21.9	28.6	
Year of diagnosis 2011–2012	13.5	48.0	24.7	34.0	
Year of diagnosis 2013–2014	14.9	51.7	33.5	37.3	
Year of diagnosis 2015–2016	23.9	66.2	45.4	58.8	

**Notes:** <sup>a</sup>Including early retirement. <sup>b</sup>Charlson Comorbidity Index<sup>23</sup> calculated from DNPR data for the 5 years preceding the FCP initiation; cerebrovascular diseases were not included in the Charlson Comorbidity Index of stroke clients; connective tissue diseases were not included in the Charlson Comorbidity Index of rheumatoid arthritis clients. **Abbreviation:** FCP, Free of charge physiotherapy.

25

FCP within 2 months of their diagnosis. FCP was mainly initiated within 2 years of the first hospital diagnosis. The overall CIP of FCP 2 years after the first hospital diagnosis was 8% (95% Confidence Interval (CI), 8–9%)) for stroke, 53% (95% CI; 52–54%) for PD, 49% (95% CI, 48–51%) for MS, and 16% (95% CI, 16–17%) for RA (Table 2). The CIP among patients not receiving FCP before the hospital diagnosis was lower (Table S1).

Patients with mild Stroke (transischemic attack and arterial syndrome) had the lowest CIP within subdiagnoses of stroke (Figure S1).

The overall CIP from 2011 to 2016 was similar or higher compared with the CIP from 2007 to 2010 (eg, the two-year CIP for patients diagnosed with PD from 2007 to 2008 and from 2015 to 2016 was 45% and 58%, respectively (Figure 1)). Looking only at patients not receiving FCP before the hospital diagnosis, only PD patients had higher CIP in the later period compared with the earlier period (Figure 1B).

The CIP among RA patients diagnosed between 2015 and 2016 was lower compared with previous years (Figure 1A and B). The CIP among those diagnosed with RA or PD in 2007 was lower compared with later years (Figure S2).

## Discussion

Using population-based, nationwide registers, we found that FCP was mainly initiated within the first 2 years after the first hospital diagnosis of stroke, PD, MS or RA. The two-year proportion of FCP was highest in PD (53%) and MS (49%) patients and lowest in RA (16%) and stroke (8%) patients. The proportion of patients referred to FCP generally increased over the period of study, especially in patients with PD and MS.

To our knowledge, this is the first study to report on the incidence of FCP in chronic disease. The study has some

limitations. Firstly, we excluded patients with two or more diseases. As these patients presumably had lower functional ability due to multi-morbidity, this exclusion may have resulted in an underestimation of the number of patients being referred for FCP. Secondly, some patients may have received municipal physiotherapy under the law of social services. As patients are not allowed to receive both FCP and municipal physiotherapy, we ideally should have included these patients as having competing events to reduce the potential underestimation of FCP. However, data on municipal physiotherapy have not been systematically recorded in the 98 municipalities in Denmark.

Third, we were unable to identify and include patients not registered in the DNPR. These patients, if any, would likely have a higher functional ability (as they were not hospitalized) and thus not require FCP. Excluding these patients may have resulted in an overestimation of the number of patients being referred for FCP. Another potential overestimation could have occurred if patients were diagnosed in the hospital before 1998 and not hospitalized in the subsequent period between 1998 and 2007 (the period used to define incident patients from 2007). However, hospitalization is likely in stroke, PD, MS and RA patients, and therefore the risk of overestimating the number of patients with FCP after incident hospital diagnosis is minimal. Finally, it should be noted that the year of incident hospital diagnosis may not reflect the true year of diagnosis, as some patients may have first been diagnosed outside the hospital, eg, by a primary care medical specialist. This applies particularly to patients with PD and MS, which may explain our finding that these patients were the quickest to begin FCP. Overall it makes good sense that FCP was mainly initiated within the first 2 years of diagnosis. A reason for late initiation could be increased disability over time.

Time Since Incident Hospital Diagnosis	Stroke	Stroke		PD		MS		RA		
	n*	CIP, % 95% CI)	n*	CIP, % (95% CI)	n*	CIP, % (95% CI)	n*	CIP, % (95% CI)		
6 months	115,262	3.4 (3.3–3.5)	4136	34.5 (33.4–35.7)	4099	29.9 (28.7–31.0)	14,277	8.9 (8.5–9.4)		
l year	102,022	6.1 (6.0-6.2)	3229	43.8 (42.6-45.0)	3353	40.1 (38.8–41.3)	13,260	.9 (  .4– 2.4)		
2 years	82,607	8.4 (8.2-8.5)	2147	52.9 (51.7–54.1)	2550	49.2 (47.9–50.5)	11,197	16.1 (15.5–16.7)		
3 years	67,181	9.6 (9.3–9.6)	1500	57.4 (56.3–58.7)	2047	54.3 (53.0–55.6)	9353	19.3 (18.6–19.9)		
4 years	54,009	10.2 (10.1–10.4)	1050	60.4 (59.2–61.6)	1599	58.2 (56.9–59.6)	7707	21.6 (20.9–22.3)		
5 years	42,269	10.9 (10.7-11.0)	698	63.1 (61.9–64.3)	1259	61.1 (59.8–62.5)	6230	23.3 (22.6–24.0)		
	1	1	1	1						

Table 2 Cumulated Incidence Proportion of FCP 6 Months to 5 Years After Incident Hospital Diagnoses of Stroke, Parkinson'sDisease (PD), Multiple Sclerosis (MS) and Rheumatoid Arthritis (RA) Between 2007 and 2016

Note: n\*, Number at risk.

26

Abbreviations: FCP, Free of charge physiotherapy; CIP, cumulated incidence proportion; CI, confidence interval.

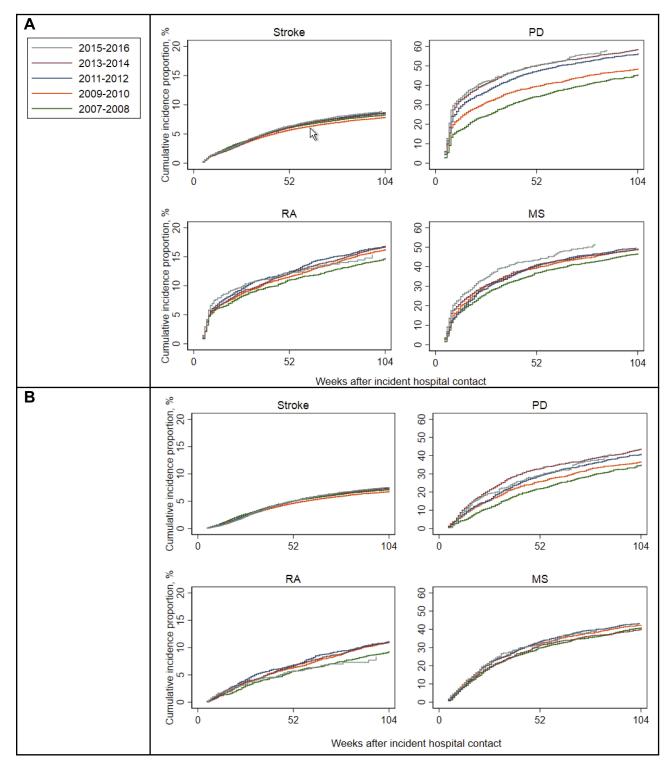


Figure I Cumulative incidence proportion of FCP after incident hospital diagnoses of stroke, Parkinson's Disease (PD), Multiple Sclerosis (MS) and Rheumatoid Arthritis (RA) by calendar year of diagnosis. (A) Overall. (B) Among those not receiving FCP before the hospital diagnosis.

A possible explanation for the low proportion of stroke patients referred to FCP is that the majority of patients had little or no functional disability following their stroke and thus did not require FCP. This was illustrated in patients with mild stroke (eg, transient ischemic attack) who had the lowest incidence of FCP indicating that FCP is related to disease severity. Another reason could be successful acute treatment (thrombolysis).<sup>16</sup> A reason for the delayed referral of stroke patients to FCP may be that patients who have suffered a stroke commonly receive hospital and/or

27

municipality-based rehabilitation for the first year afterwards.<sup>17</sup> The findings that stroke patients had fewer and slower referrals to FCP compared to the other groups and high mortality rate raise the question of whether a more active approach in stroke patients could help to reduce the mortality in this population.<sup>18,19</sup> The proportion of RA patients referred to FCP was only slightly higher than stroke patients and substantially lower than PD and MS patients. This is surprising, since RA, unlike a stroke but like PD and MS, is a progressive disease. However, patients with RA are being increasingly well treated with medication.<sup>20</sup> Therefore, RA patients decreased the incidence of FCP in the latest study period may indicate a reduced need for physiotherapy.

In patients with PD and MS, the proportion of patients receiving FCP increased over the period of study. This increase could partly be due to the growing amount of evidence over recent years showing the positive effects of training in PD and MS patients.<sup>21,22</sup> Another reason for the increased incidence of FCP over the study period may be the change in legislation in August 2008, which enabled less severe disabled patients to be referred to FCP. The very low CIP in patients diagnosed with PD in 2007 indicates the immediate effect of the legislative changes in this patient group (Figure S2).

The finding of similar rates of FCP over the study period among the MS patients not receiving FCP before the hospital diagnosis (Figure 1B) indicates that the rise of FCP in this patient group was mostly due to more patients being diagnosed and referred from primary care.

The current study included patients with diagnoses registered by hospital medical specialists in the DNPR. However, patients may be referred to FCP by a primary care medical specialist due to other diagnoses. Therefore, the hospital diagnoses in the DNPR do not necessarily correspond to the FCP referral diagnoses, registered in the DHSR. Future studies should investigate the agreement between the diagnoses from the DNPR and the diagnoses for which the patients receive FCP.

The finding of the very low incidence of FCP in patients with mild stroke indicates that FCP is related to disease severity. Future studies should retrieve data on the degree of severity or dependence from the clinical quality databases for stroke, MS and RA, to explore the incidence of referral within different degrees of dependence.

# Conclusion

28

In the current cohort, we found that FCP was mainly initiated within the first 2 years after the first hospital diagnosis of stroke, PD, MS or RA. The two-year proportion of FCP was highest in patients with PD and MS and the proportion of patients referred to FCP generally increased over the period of study.

### Abbreviations

CI, Confidence Interval; CIP, Cumulated Incidence Proportion; FCP, Free of Charge Physiotherapy; MS, Multiple Sclerosis; PD, Parkinson's Disease; RA, Rheumatoid Arthritis; RR, Risk Ratio; DNPR, the Danish National Patient Registry; DHSR, the National Health Service Registry.

## **Data Sharing Statement**

As part of the Data Use Agreement at Statistics Denmark, authors are not allowed to provide raw data. Upon reasonable request, the corresponding author will provide statistical programming codes used to generate the results.

## Funding

The project was funded by "Foundation of research, quality and education in practical physiotherapy", Denmark.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- 1. Boehmer KR, Gionfriddo MR, Rodriguez-Gutierrez R, et al. Patient capacity and constraints in the experience of chronic disease: a qualitative systematic review and thematic synthesis. *BMC Fam Pract.* 2016;17(127). doi:10.1186/s12875-016-0525-9
- Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: the stroke recovery and rehabilitation roundtable taskforce. *Neurorehabil Neural Repair*. 2017;31(9):793–799. doi:10.1177/ 1545968317732668
- Horstinka M, Tolosab E, Bonuccellic U, et al. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies and the Movement Disorder Society–european Section. Part I: early (uncomplicated) Parkinson's disease. *Eur J Neurol.* 2006;13(1):1170–1185. doi:10.1111/j.1468-1331.2006.01547.x
- Khan F, Amatya B. Rehabilitation in multiple sclerosis: a systematic review of systematic reviews. *Neuropsychologia*. 2017;98:353–367.
- Wevers L, Van De Port I, Vermue M, Mead G, Kwakkel G. Effects of task-oriented circuit class training on walking competency after stroke: a systematic review. *Stroke*. 2009;40(7):2450–2459. doi:10.1161/ STROKEAHA.108.541946
- Notthoff N, Reisch P, Gerstorf D. Individual characteristics and physical activity in older adults: a systematic review. *Gerontology*. 2017;63(5):443–459. doi:10.1159/000475558
- Sundhedsstyrrelsen. National board of health in Denmark. 2019. Available from: https://www.sst.dk/da/udgivelser/2019/vejledning-omadgang-til-vederlagsfri-fysioterapi. Accessed January 23, 2019.

- Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health*. 2011;39(7):12–16. doi:10.1177/1403494811399956
- Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National patient registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490. doi:10.2147/CLEP.S91125
- Sahl Andersen J, De Fine Olivarius N, Krasnik A. The Danish national health service register. *Scand J Public Health*. 2011;39 (7):34–37. doi:10.1177/1403494810394718
- Pedersen CB. The Danish civil registration system. Scand J Public Health. 2011;39(7):22–25. doi:10.1177/1403494810387965
- Wildenschild C, Mehnert F, Thomsen RW, et al. Registration of acute stroke: validity in the Danish stroke registry and the Danish national registry of patients. *Clin Epidemiol.* 2013;6(1):27–36. doi:10.2147/ CLEP.S50449
- Mason K, Thygesen LC, Stenager E, Brønnum-Hansen H, Koch-Henriksen N. Evaluating the use and limitations of the Danish National Patient Register in register-based research using an example of multiple sclerosis. *Acta Neurol Scand.* 2012;125(3):213–217. doi:10.1111/j.1600-0404.2011.01558.x
- Wermuth L, Lassen CF, Himmerslev L, Olsen J, Ritz B. Validation of hospital register-based diagnosis of Parkinson 's disease. *Dan Med J*. 2012;59(3):A4391.
- 15. Ibfelt EH, Sørensen J, Jensen DV, et al. Validity and completeness of rheumatoid arthritis diagnoses in the nationwide DANBIO clinical register and the Danish national patient registry. *Clin Epidemiol.* 2017;9:627–632. doi:10.2147/CLEP.S141438
- 16. Kaesmacher J, Dobrocky T, Heldner MR, et al. Systematic review and meta-analysis on outcome differences among patients with TICI2b versus TICI3 reperfusions: success revisited. *J Neurol Neurosurg Psychiatry*. 2018;89(9):910–917. doi:10.1136/jnnp-2017-317602

- Kristensen HK, Ytterberg C, Jones DL, Lund H. Research-based evidence in stroke rehabilitation: an investigation of its implementation by physiotherapists and occupational therapists. *Disabil Rehabil*. 2016;38(26):2564–2574. doi:10.3109/09638288.2016.1138550
- Kraus WE, Janz KF, Powell KE, et al. Daily step counts for measuring physical activity exposure and its relation to health. *Med Sci Sports Exercise*. 2019;51(6):1206–1212. doi:10.1249/MSS.000000 0000001932
- Amadid H, Johansen NB, Bjerregaard AL, et al. The role of physical activity in the development of first cardiovascular disease event: a tree-structured survival analysis of the Danish ADDITION-PRO cohort. *Cardiovasc Diabetol.* 2018;17(1):1–12. doi:10.1186/s12933-018-0769-x
- Stoffer MA, Schoels MM, Smolen JS, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. *Ann Rheum Dis.* 2016;75(1):16–22. doi:10.1136/annrheumdis-2015-207526
- Negaresh R, Motl RW, Zimmer P, Mokhtarzade M, Baker JS. Effects of exercise training on multiple sclerosis biomarkers of central nervous system and disease status: a systematic review of intervention studies. *Eur J Neurol.* 2019;26(5):711–721. doi:10.1111/ene.2019.26. issue-5
- 22. Perry SIB, Nelissen PM, Siemonsma P, Lucas C. Complementary therapies in medicine the effect of functional-task training on activities of daily living for people with Parkinson's disease, a systematic review with meta-analysis. *Complement Ther Med.* 2019;42 (September2018):312–321. doi:10.1016/j.ctim.2018.12.008
- Charlson M, Pompei P, Ales K, Mackenzei C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373–383. doi:10.1016/0021-9681(87)90171-8

#### **Clinical Epidemiology**

#### **Dove**press

29

#### Publish your work in this journal

Clinical Epidemiology is an international, peer-reviewed, open access, online journal focusing on disease and drug epidemiology, identification of risk factors and screening procedures to develop optimal preventative initiatives and programs. Specific topics include: diagnosis, prognosis, treatment, screening, prevention, risk factor modification,

Submit your manuscript here: https://www.dovepress.com/clinical-epidemiology-journal

systematic reviews, risk & safety of medical interventions, epidemiology & biostatistical methods, and evaluation of guidelines, translational medicine, health policies & economic evaluations. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use.