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ORIGINAL RESEARCH

# Frozen Shoulder and the Risk of Parkinson's Disease: A Danish Registry-Based Cohort Study

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**Background:** Frozen shoulder may be an early preclinical symptom of Parkinson's disease (PD).

**Objective:** To examine PD risk after frozen shoulder diagnosis and to evaluate this disorder as a possible manifestation of parkinsonism preceding the clinical recognition of PD and possible target for screening.

**Methods:** Danish population-based medical registries were used to identify patients aged ≥40 years with a first-time frozen shoulder diagnosis (1995–2016). A comparison cohort was randomly selected from the general population matched on age and sex. To address detection bias and the specificity of frozen shoulder diagnosis, we performed a sensitivity analysis, using similar matching criteria to select a cohort of patients with back pain diagnosis. The outcome was incident PD. Cumulative incidences and adjusted hazard ratios (HRs) were estimated with 95% confidence intervals (CIs).

**Results:** We identified 37,041 individuals with frozen shoulder, 370,410 general population comparators, and 111,101 back pain comparators. The cumulative incidence of PD at 0–22 years follow-up was 1.51% in the frozen shoulder cohort, 1.03% in the general population cohort, and 1.32% in the back pain cohort. For frozen shoulder versus general population, adjusted HRs were 1.94 (CI: 1.20–3.13) at 0–1 years and 1.45 (CI: 1.24–1.70) at 0–22 years follow-up. For frozen shoulder versus back pain, adjusted HRs were 0.89 (CI: 0.54–1.46) and 1.01 (CI: 0.84–1.21), respectively.

**Conclusion:** Patients with frozen shoulder had an increased PD risk compared with the general population, although the absolute risks were low. Frozen shoulder might sometimes represent early manifestations of PD. Detection bias probably cannot account for the increased PD risk during the long-term follow-up.

**Keywords:** adhesive capsulitis, back pain, cohort studies, frozen shoulder, Parkinson disease

## Introduction

Adhesive capsulitis, also known as frozen shoulder, is an inflammatory condition of the shoulder joint affecting the synovial membrane and the capsule.[1] The population prevalence is estimated at 2–5%.[2] The diagnosis is based on symptoms of shoulder pain and stiffness, resulting in restriction of the normal range of movement of the shoulder.[3] Trauma, operation, or immobilization frequently precedes the onset of disease,[4] and diabetes as well as female sex are overrepresented in patients with frozen shoulder.[5,6] The usually spontaneous remission may occur after several months to years.[3] Shoulder pain and diagnosis of frozen shoulder have been frequently observed in patients with Parkinson's disease (PD).[7–10] PD is a degenerative disorder of the central nervous system resulting in progressive motor symptoms, often preceded and accompanied by non-motor symptoms. The cardinal signs of Parkinson's disease are bradykinesia, rigidity and tremor;[11] postural instability is often present as well. PD affects approximately 1% of the population above 60 years of age.[12] The mean duration of PD diagnosis until death is 6.9 to 14.3 years.[13] PD is progressive in its course and treatment is symptomatic, mostly aiming at diminishing the motor symptoms of the disease. Although disease-modifying drugs are not yet available, early diagnosis can lead to symptomatic treatment, guide long-term planning, and help identify individuals most appropriate for prevention and trials of disease-modifying therapies.

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Between 40% and 95% of PD patients report pain, including musculoskeletal pain such as shoulder or back pain.[14–16] Rigidity, prolonged immobilization, and postural changes associated with the progression of PD have been suggested as contributing to the development of shoulder pain or stiffness in PD patients.[17–19] A recent review covered a number of aspects behind shoulder issues in patients with PD.[20] With shoulder pain and stiffness being cardinal symptoms of frozen shoulder, patients presenting with these symptoms may be diagnosed with frozen shoulder although the symptoms represent early symptoms of preclinical PD, which is supported by the findings of previous studies.[20]

However, evidence is limited to case-control studies,[20] the first one of which in 1989 found peak of frozen shoulder to occur 2 years before diagnosis of PD.[21] Past or present symptoms of shoulder pain and stiffness as well as other musculoskeletal pains have been investigated in relation to PD in a small number of case-control studies since then.[8,22] A more recent case-control study evaluated 146 patients suspected of PD and reported odds ratio of 3.1 for PD diagnoses among those with frozen shoulder in this selected population.[23] To summarize, although previous studies suggest high prevalence of frozen shoulder or related symptoms in patients with PD, it remains unclear whether frozen shoulder should be considered an early preclinical manifestation and important predictor of PD and whether diagnoses of frozen shoulders have the potential as a target for PD screening. Therefore, we performed a cohort study, examining the risk of incident PD following a first-time diagnosis of frozen shoulder using nationwide data from Danish population-based medical registries.

# Method

## Data Sources

This population-based cohort study was conducted using prospectively collected Danish data from nationwide medical registries. Denmark has a population of approximately 5.8 million people,[24] and all residents have access to tax-supported public healthcare. All Danish residents are at birth or immigration assigned a unique personal identification number, which enables the linking of data between registries at the individual level.

Data were collected from the Danish National Patient Registry (DNPR) and the Danish Civil Registration System (DCRS). The DCRS was established in 1968 and contains information on the date of birth, sex, migration, and date of death of all Danish residents.[25]

The DNPR has since 1977 recorded all hospitalizations in Denmark, and since 1995 all outpatient clinic contacts as well.[26] During 1977–1993 diagnoses were classified by the International Classification of Disease 8th Edition (ICD-8), but since 1994 the 10th edition (ICD-10) has been used.

## Study Cohorts

From the DNPR, all patients with a first-time hospital-based diagnosis of frozen shoulder (inpatient or hospital outpatient clinic) from January 1, 1995, to November 30, 2016, were identified. Both primary and secondary diagnoses were included. Patients under the age of 40 years and those with a PD diagnosis prior to or on the day of a frozen shoulder diagnosis (ie the index date) were excluded.

Using DCRS and DNPR, a cohort from the general population was established for comparison. To explore frozen shoulder as a specific preclinical manifestation of PD and address possible detection bias, a cohort of patients diagnosed with back pain was also established for use in sensitivity analysis. Back pain is comparable to frozen shoulder in that it likewise represents a musculoskeletal condition frequently occurring in patients with PD,[27,28] while having distinct diagnosis codes, and being frequent enough among the general population to enable an adequate number of patients eligible for inclusion. Like the frozen shoulder cohort, patients from the back pain cohort had contact with the hospital, theoretically increasing the likelihood of detection of PD, and therefore we suspect a risk of detection bias in this cohort as well. Thereby, if results showed that frozen shoulder was a stronger risk factor than back pain for PD, this would support that our results for the frozen shoulder cohort were not solitary due to detection bias. For each patient with a frozen shoulder, up to 10 persons from the general population and up to three persons with an incident diagnosis of back pain within 1 year prior to the index date of their matched pair were randomly selected. The comparators did not have a previous diagnosis of frozen shoulder or PD and were matched with replacement on sex and year of birth for the

individuals in the frozen shoulder cohort. The follow-up for the comparators started at the index date of frozen shoulder patients to which they were matched. Individuals in the two comparison cohorts were eligible for inclusion in the frozen shoulder cohort if they sustained a frozen shoulder during follow-up, in which case they started contributing time to the frozen shoulder cohort with their own matched comparison set. For diagnosis codes see Supplementary Appendix.

## Variables

Information on sex and age was obtained from the DCRS. Data on all available inpatient and outpatient discharge diagnoses since 1977 were collected from DNPR to ascertain the comorbidity history of the cohorts. For confounder adjustment, information on the following diagnoses were collected: autoimmune disease, chronic obstructive pulmonary disease, thyroid disease, dementia, and diabetes.[6,29–34] For diagnosis codes and surgery codes see Supplementary Appendix.

## Outcome

Information on PD diagnosis after the index date was obtained using the DNPR for all three cohorts. PD outcome was defined using hospital-based diagnoses from inpatient and outpatient contacts, excluding diagnoses from emergency room visits because of the assumed low validity. Both primary and secondary PD diagnosis codes were used in this study. For diagnosis codes see Supplementary Appendix.

## Statistical methods

The prevalence of baseline patient characteristics of the three cohorts as of the index date was tabulated.

All individuals were followed from the index date until the diagnosis of PD, emigration, loss of follow-up, death, or the end of the study period (November 30, 2016), whichever occurred first. To estimate the short-term, long-term, and total risk of PD, multiple periods at different cut-offs were defined for the total period: 1, 3, 6, and 10 years.

Thus, the cumulative incidence of PD was calculated for all three cohorts using the cumulative incidence method while considering death as a competing risk and reported at follow-up of 0–1 year, 1–3 years, 1–6 years, 1–10 years, 1–22 years, and 0–22 years.[35] Median follow-up time until PD diagnosis was calculated as well. From the cumulative incidences, the number needed to screen was calculated as 1 divided by the absolute risk reduction.

Incidence rates of PD per 1000-person-years during the total follow-up period (0–22 years), as well as for 0–1 year, 1–3 years, 3–6 years, 6–10 years, 10–22 years, and 1–22 years of follow-up, were estimated. Hazard ratios (HR), including 95% confidence intervals (CIs), were estimated for the association between frozen shoulder and PD using Cox proportional hazard regression.HRs were calculated both unadjusted and adjusted for chronic obstructive pulmonary disease, autoimmune disease, thyroid disease, dementia, and diabetes. To further address detection bias, adjusted HRs were calculated additionally, adjusting for further comorbidities using the Charlson comorbidity index, excluding chronic pulmonary disease, autoimmune disease, and dementia from the index, as these comorbidities were adjusted for individually.[36] Analyses on incidence rate and HR were performed overall and stratified by age and sex.

Death, emigration, loss to follow-up, PD, or the end of the study led to censoring in the analysis.

The content of this paper follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the REporting of studies Conducted using Observational Routinely collected Data (RECORD) guidelines.[37,38] Analyses were performed using SAS V. 9.4 (SAS Institute Inc., Cary, NC, USA) and R (version 3.6.1; R Foundation for Statistical Computing).

# Results

## Characteristics of Participants

From 1995 to 2016, we identified 37,041 frozen shoulder patients over the age of 40 years, as well as 370,410 general population comparators and 111,101 back pain comparators. Table 1 presents the characteristics of the three cohorts.

In the frozen shoulder cohort, most patients were women and between the ages of 40 and 59 years.

The similar distributions of sex and age in the three cohorts suggested successful matching.

**Table 1** Characteristics of the Frozen Shoulder Cohort, the General Population Comparison Cohort, and the Back Pain Comparison Cohort

| | Frozen Shoulder Cohort | General Population Cohort | Back Pain Cohort |
|---|---|---|---|
| **No. of observations** | 37,041 (100.0) | 370,410 (100.0) | 111.101 (100.0) |
| **Sex** | | | |
| Male | 15,991 (43.2) | 159,910 (43.2) | 47,962 (43.2) |
| Female | 21,050 (56.8) | 210,500 (56.8) | 63,139 (56.8) |
| **Age in years** | | | |
| 0–39 | | 973 (0.3) | 317 (0.3) |
| 40–59 | 25,311 (68.3) | 252,003 (68.0) | 75,580 (68.0) |
| 60–69 | 7,700 (20.8) | 77,070 (20.8) | 23,130 (20.8) |
| 70–79 | 2995 (8.1) | 29,959 (8.1) | 8983 (8.1) |
| 80 + | 1035 (2.8) | 10,405 (2.8) | 3091 (2.8) |
| **Index year** | | | |
| 1995–2004 | 9403 (25.4) | 94,030 (25.4) | 28,196 (25.4) |
| 2005–2013 | 18,884 (51.0) | 188,840 (51.0) | 56,646 (51.0) |
| 2014–2016 | 8754 (23.6) | 87,540 (23.6) | 26,259 (23.6) |
| **Type of hospital diagnosis of frozen shoulder** | | | |
| Primary diagnosis | 33,237 (89.7) | – | – |
| Secondary diagnosis | 3804 (10.3) | – | – |
| Inpatient | 2765 (7.5) | – | – |
| Outpatient | 34,173 (92.3) | – | – |
| Half day patient | 103 (0.3) | – | – |
| **Comorbidities** | | | |
| Chronic obstructive pulmonary disease | 2368 (6.4) | 17,633 (4.8) | 10,953 (9.9) |
| Myocardial infarction | 1108 (3.0) | 7875 (2.1) | 3665 (3.3) |
| Stroke | 1481 (4.0) | 10,906 (2.9) | 5249 (4.7) |
| Thyroid disease | 1091 (2.9) | 7878 (2.1) | 3632 (3.3) |
| Shoulder trauma | 10,696 (28.9) | 17,076 (4.6) | 11,300 (10.2) |
| Shoulder surgery | 5794 (15.6) | 8935 (2.4) | 5747 (5.2) |
| Autoimmune disease | 4238 (11.4) | 28,803 (7.8) | 18,583 (16.7) |
| Dementia | 108 (0.3) | 1403 (0.4) | 697 (0.6) |
| Diabetes | 3987 (10.8) | 13,592 (3.7) | 6908 (6.2) |
| Congestive heart failure | 649 (1.8) | 4623 (1.2) | 2721 (2.4) |
| Peripheral vascular disease | 949 (2.6) | 6248 (1.7) | 4225 (3.8) |
| Cerebrovascular disease | 1752 (4.7) | 13,079 (3.5) | 6496 (5.8) |

(*Continued*)

**Table 1** (Continued).

| | Frozen Shoulder Cohort | General Population Cohort | Back Pain Cohort |
|---|---|---|---|
| Ulcer disease | 880 (2.4) | 6141 (1.7) | 4439 (4.0) |
| Mild liver disease | 295 (0.8) | 3020 (0.8) | 1886 (1.7) |
| Hemiplegia | 75 (0.2) | 591 (0.2) | 384 (0.3) |
| Moderate to severe renal disease | 400 (1.1) | 2908 (0.8) | 1790 (1.6) |
| Any tumor | 2040 (5.5) | 18,629 (5.0) | 7057 (6.4) |
| Leukemia | 62 (0.2) | 432 (0.1) | 209 (0.2) |
| Lymphoma | 118 (0.3) | 1174 (0.3) | 719 (0.6) |
| Moderate to severe liver disease | 63 (0.2) | 657 (0.2) | 414 (0.4) |
| Metastatic solid tumor | 181 (0.5) | 1695 (0.5) | 1104 (1.0) |
| AIDS | 26 (0.1) | 337 (0.1) | 94 (0.1) |

Comorbidities were more prevalent in the frozen shoulder cohort than in the general population cohort. Diabetes, autoimmune diseases, and COPD were more frequently observed in the frozen shoulder cohort than in the general population cohort. The back pain cohort had a higher frequency of vascular diseases, autoimmune diseases, and COPD than both the general population cohort and the frozen shoulder cohort. The back pain cohort had a higher cumulative incidence of death than the frozen shoulder cohort and the general population cohort, in which the cumulative incidences of death were similar (Figure 1).

## PD Risk

In the frozen shoulder cohort, 21 patients were diagnosed with PD 0–1 year after the index date, whereas 163 patients were diagnosed with PD 1–22 years after the index date. This corresponds to cumulative incidences of PD of 0.06% and 1.47%, respectively.

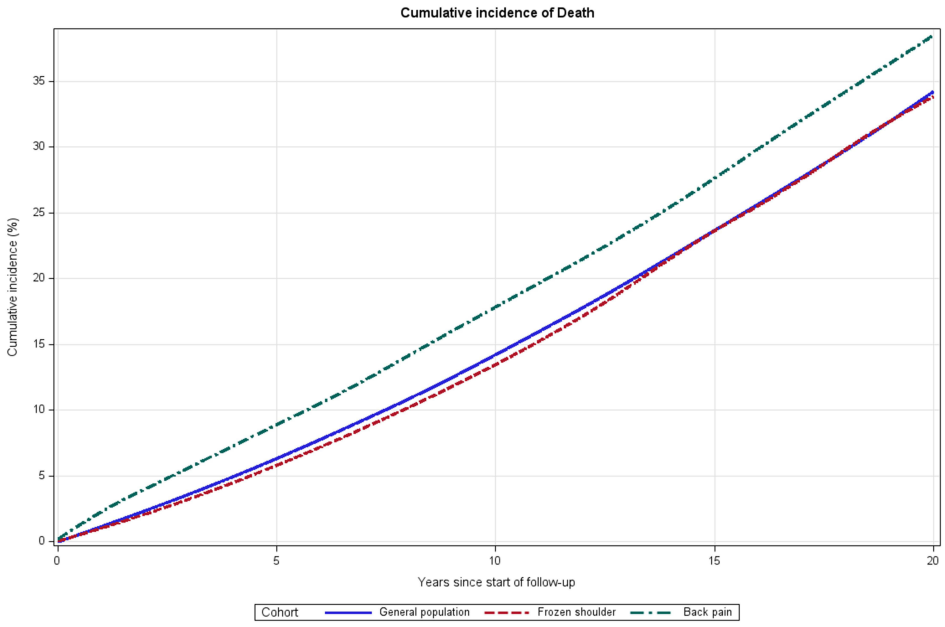


**Figure 1** Cumulative incidence plot. Cumulative incidence of death from index date and over 20 years of follow up for the cohort of population comparators, the frozen shoulder cohort, and the back pain cohort. Curves were smoothed for data protection.

In comparison, cumulative incidence in the general population cohort and in the back pain cohort was estimated to 0.03% and 0.07%, respectively, at 0–1 years follow-up and 1.01% and 1.28%, respectively, at 1–22 years follow-up. The number of events and cumulative incidence are shown in Table 2, and the cumulative incidence of PD is illustrated in Figure 2.

The median follow-up time before PD diagnosis was 5.04 years in the frozen shoulder cohort, 5.70 years in the general population cohort, and 4.55 years in the back pain cohort.

Comparing the frozen shoulder cohort to the general population cohort, the number needed to screen was −3,333 at 0–1 years follow-up and −208 at 0–22 years follow-up.

The overall incidence rates and hazard rates are presented in Table 3, and stratified analyses are presented in Supplementary Tables S1 and S2.

After adjusting for potential confounders, the adjusted HRs for PD in the frozen shoulder cohort in relation to the general population cohort were 1.94 (95% CI: 1.20–3.13) for the 0–1 year follow-up period and 1.45 (95% CI: 1.24–1.70) at 0–22 years of follow-up. The adjusted HRs for the diagnosis of PD among the frozen shoulder cohort in

**Table 2** Cumulative Incidence of Parkinson's Disease

| Follow up Period | No. of individuals at Risk at the Beginning of the Period | No. of Incident Parkinson's Disease Diagnoses | Cumulative risk (%)[a] | 95% confidence Interval (%) |
|---|---|---|---|---|
| **Frozen shoulder cohort** | | | | |
| 0–1 years | 37,041 | 21 | 0.06 | 0.04–0.09 |
| 1–3 years | 33,929 | 44 | 0.14 | 0.10–0.19 |
| 1–6 years | 33,929 | 75 | 0.27 | 0.21–0.34 |
| 1–10 years | 33,929 | 117 | 0.55 | 0.45–0.67 |
| 1–22 years | 33,929 | 163 | 1.47 | 1.15–1.85 |
| 0–22 years | 37,041 | 184 | 1.51 | 1.19–1.89 |
| **General population cohort** | | | | |
| 0–1 years | 370,410 | 101 | 0.03 | 0.02–0.03 |
| 1–3 years | 338,581 | 246 | 0.08 | 0.07–0.09 |
| 1–6 years | 338,581 | 534 | 0.20 | 0.19–0.22 |
| 1–10 years | 338,581 | 796 | 0.38 | 0.35–0.41 |
| 1–22 years | 338,581 | 1128 | 1.01 | 0.92–1.11 |
| 0–22 years | 370,410 | 1229 | 1.03 | 0.94–1.13 |
| **Back pain cohort** | | | | |
| 0–1 years | 111,101 | 71 | 0.07 | 0.05–0.08 |
| 1–3 years | 100,262 | 115 | 0.13 | 0.11–0.15 |
| 1–6 years | 100,262 | 233 | 0.30 | 0.26–0.34 |
| 1–10 years | 100,262 | 337 | 0.52 | 0.47–0.59 |
| 1–22 years | 100,262 | 450 | 1.28 | 1.11–1.48 |
| 0–22 years | 111,101 | 521 | 1.32 | 1.15–1.51 |

**Note**: [a]Treating death as a competing risk.

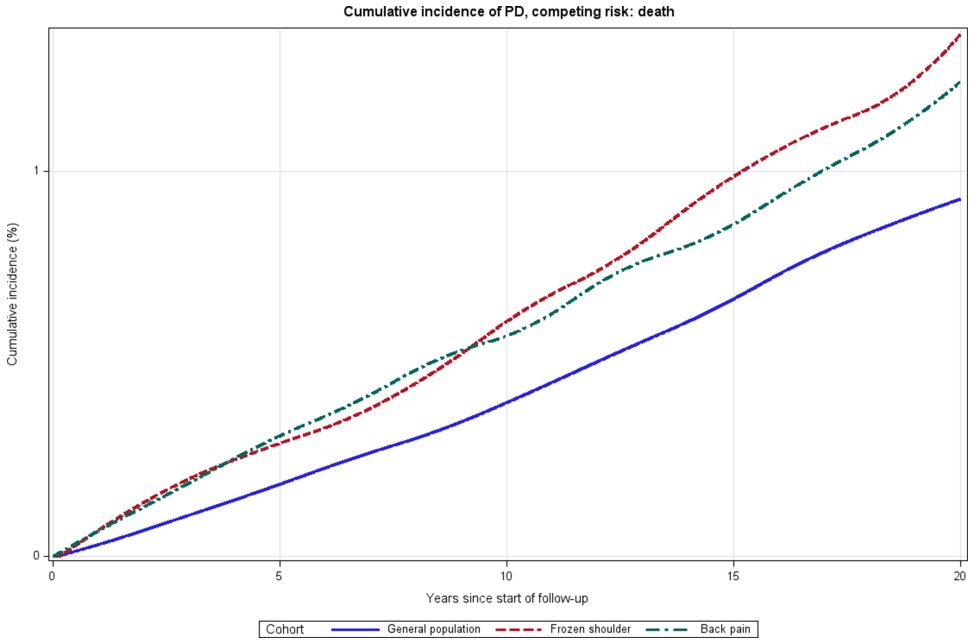


**Figure 2** Cumulative incidence plot. Cumulative incidence Parkinson's disease from index date and over 20 years of follow up for the cohort of population comparators, the frozen shoulder cohort, and the back pain cohort. Curves were smoothed for data protection.

comparison to the back pain cohort were 0.89 (95% CI: 0.54–1.46) for the 0–1 year follow-up period and 1.01 (95% CI: 0.84–1.21) at 0–22 years follow-up (Table 3).

Additional adjustments for other comorbidities using the Charlson Comorbidity Index did not substantially change the estimates (Table 3).

The results of the analyses stratified by sex and age are presented in Supplementary Tables S1 and S2.

In both the frozen shoulder cohort and the general population cohort, the estimated incidence rates of PD were higher among males than females. At 0–1 year follow-up adjusted HRs were higher for males, but at 1–3 years of follow-up the adjusted HRs were higher for females. Upon age stratification, the estimated incidence rates were highest among those age 70–79 years, while the adjusted HRs were highest among those age 60–69 years.

# Discussion

In this large population-based cohort study of 37,041 patients with frozen shoulder diagnoses, we found an increased risk of PD diagnosis at short- and long-term follow-up when comparing to a general population cohort. The relative risk was particularly high during the first year after incident frozen shoulder diagnosis.

## Interpretation and Comparison

A few previous studies on shoulder pain in patients with PD or on the association between frozen shoulder and PD were mostly case-control studies except from one cross-sectional study.[8–10,21–23,39,40] One study from 1989 found among 150 Parkinson's disease cases that 19 cases (13%) had a prior diagnosis of frozen shoulder or a history of symptoms interpreted by the authors as frozen shoulder.[21] Of these 19 patients, 11 (58%) reported that the onset of shoulder symptoms occurred 0–2 years before their Parkinson's disease diagnosis. The largest case-control study on this topic, involving 8,166 cases and 46,755 controls in the UK and using a primary care registry, suggested that PD patients have 35% increased risk for symptoms of shoulder pain and stiffness 2 years prior to PD diagnosis when compared with non-PD controls.[22] However, they found no increased risk 5 years prior to PD diagnosis.

Previous studies were limited by small study size, selection issues, possible recall bias, and some were conducted more than 30 years ago. Cross-sectional design is not appropriate to evaluate risk factors, either on a relative or absolute scale, because information on frozen shoulder and PD is collected at the same time. Although, if performed properly, odds ratios may be estimated using a case-control design to evaluate frozen shoulder as a risk factor on a relative scale,

**Table 3** Incidence Rates and Hazard Ratios for Parkinson's Disease, Comparing the Frozen Shoulder Cohort to the General Population and Back Pain Cohorts

| | Follow-up Period | No. of Incident Parkinson's Disease Diagnoses [a] | Incidence Rate (per 1000PYRs) (95% CI) | Unadjusted Hazard Ratio (95% CI) | Adjusted Hazard Ratio (95% CI) [b] | Adjusted Hazard Ratio (95% CI) [c] |
|---|---|---|---|---|---|---|
| **FROZEN SHOULDER COHORT VS GENERAL POPULATIO COHORT** | **General population cohort** | | | | | |
| | 0–1 year | 100 | 0.28 (0.23–0.34) | - | - | - |
| | 1–3 years | 245 | 0.41 (0.36–0.46) | - | - | - |
| | 3–6 years | 290 | 0.43 (0.38–0.48) | - | - | - |
| | 6–10 years | 260 | 0.48 (0.42–0.54) | - | - | - |
| | 10–22 years | 330 | 0.69 (0.61–0.76) | - | - | - |
| | 1–22 years | 1130 | 0.49 (0.46–0.52) | - | - | - |
| | 0–22 years | 1230 | 0.46 (0.44–0.49) | - | - | - |
| | **Frozen shoulder cohort** | | | | | |
| | 0–1 year | 20 | 0.59 (0.37–0.87) | 2.09 (1.31–3.35) | 1.94 (1.20–3.13) | 1.92 (1.19–3.12) |
| | 1–3 years | 45 | 0.72 (0.53–0.95) | 1.79 (1.30–2.48) | 1.78 (1.28–2.46) | 1.77 (1.28–2.46) |
| | 3–6 years | 30 | 0.46 (0.31–0.64) | 1.08 (0.74–1.57) | 1.04 (0.71–1.52) | 1.04 (0.71–1.52) |
| | 6–10 years | 40 | 0.77 (0.55–1.01) | 1.66 (1.19–2.32) | 1.62 (1.15–2.27) | 1.60 (1.14–2.25) |
| | 10–22 years | 45 | 0.96 (0.71–1.26) | 1.34 (0.97–1.84) | 1.26 (0.91–1.75) | 1.28 (0.92–1.78) |
| | 1–22 years | 165 | 0.71 (0.60–0.82) | 1.44 (1.22–1.71) | 1.40 (1.19–1.66) | 1.40 (1.18–1.66) |
| | 0–22 years | 185 | 0.69 (0.60–0.80) | 1.50 (1.28–1.76) | 1.45 (1.24–1.70) | 1.44 (1.23–1.69) |
| **FROZEN SHOULDER COHORT VS BACK PAIN COHORT** | **Back pain cohort** | | | | | |
| | 0–1 year | 70 | 0.67 (0.53–0.84) | - | - | - |
| | 1–3 years | 115 | 0.64 (0.53–0.77) | - | - | - |
| | 3–6 years | 120 | 0.61 (0.51–0.73) | - | - | - |
| | 6–10 years | 105 | 0.67 (0.55–0.80) | - | - | - |
| | 10–22 years | 115 | 0.84 (0.69–1.00) | - | - | - |
| | 1–22 years | 450 | 0.68 (0.62–0.74) | - | - | - |
| | 0–22 years | 520 | 0.68 (0.62–0.74) | - | - | - |
| | **Frozen shoulder cohort** | | | | | |
| | 0–1 year | 20 | 0.59 (0.37–0.87) | 0.87 (0.53–1.41) | 0.89 (0.54–1.46) | 0.94 (0.56–1.58) |
| | 1–3 years | 45 | 0.72 (0.53–0.95) | 1.09 (0.77–1.55) | 1.09 (0.76–1.55) | 1.08 (0.75–1.56) |
| | 3–6 years | 30 | 0.46 (0.31–0.64) | 0.75 (0.50–1.14) | 0.76 (0.50–1.15) | 0.77 (0.50–1.17) |
| | 6–10 years | 40 | 0.77 (0.55–1.01) | 1.17 (0.80–1.71) | 1.20 (0.81–1.76) | 1.25 (0.84–1.86) |
| | 10–22 years | 45 | 0.96 (0.71–1.26) | 1.14 (0.78–1.67) | 1.24 (0.82–1.87) | 1.26 (0.83–1.90) |
| | 1–22 years | 165 | 0.71 (0.60–0.82) | 1.03 (0.85–1.24) | 1.03 (0.85–1.25) | 1.04 (0.86–1.26) |
| | 0–22 years | 185 | 0.69 (0.60–0.80) | 1.01 (0.84–1.20) | 1.01 (0.84–1.21) | 1.02 (0.85–1.22) |

**Notes**: [a] Rounded to nearest 5, [b] Adjusted for chronic obstructive pulmonary disease, autoimmune disease, thyroid disease, dementia, and diabetes, [c] Adjusted for chronic obstructive pulmonary disease, autoimmune disease, thyroid disease, dementia, diabetes, and Charlson comorbidity index.
**Abbreviations**: PYRs, Person-years; CI, Confidence interval.

case-control design is not fit for evaluating incidence of PD among patients with frozen shoulder as we have done in our study. Therefore, the previous literature lacks an evaluation of frozen shoulder as a risk factor on an absolute scale. Incidence or absolute risks are important to consider when evaluating the clinical impact of a risk factor and the appropriateness of targeted screening.

Our results suggest that individuals with frozen shoulder have a higher chance of being diagnosed with PD than the general population, with the risk persisting for up to 22 years. However, although our cohort design obviated recall bias, detection bias was a concern. Our frozen shoulder cohort had a higher frequency of comorbidities than did the general population cohort. Patients seen at the hospital with frozen shoulders or any of their comorbidities may have other early PD-related symptoms. Thus, the observed increased risk of PD in patients with frozen shoulder compared with the general population might be caused by a higher chance of (early) diagnosis rather than a higher risk of developing the disease.

To address detection bias and the possible specificity of frozen shoulder as an early preclinical musculoskeletal manifestation of PD in sensitivity analysis, we compared the frozen shoulder cohort to a cohort of patients with hospital-diagnosed back pain, a different musculoskeletal issue that would also increase the likelihood of medical assessment. Back pain may be comparable to frozen shoulder, as it also occurs frequently among PD patients.[27,28] Furthermore, patients referred to a hospital for back pain could be more likely to undergo neurological assessment than patients with frozen shoulder to rule out disorders of the spinal cord. However, we did not perform analysis of back pain as a primary exposure by comparing the back pain cohort to the general population cohort, as we suspected back pain to likely be too unspecific to be a proper tool for prediction of PD as back pain is a common symptom in the general population with heterogeneous etiology.

Notably, a study from 2015 reported an increased risk of a history of frozen shoulder in PD cases compared to controls but found no increased risk of a history of back pain.[22]

Overall, the frozen shoulder cohort had a similar prevalence of comorbidities to the back pain cohort, although the distribution of individual comorbidities varied. Of the three cohorts, the back pain cohort had the highest frequency of COPD, whereas the general population cohort had the lowest frequency. COPD is highly associated with smoking,[41] but there is an inverse relationship between smoking and the risk of PD.[34] We adjusted for COPD as a proxy for smoking, but this approach only partially adjusts for smoking, and we suspect some residual confounding. The back pain cohort also had a higher cumulative incidence of death than the other two other cohorts; thus, death represents a major competing risk in both short- and long-term follow-up. The higher cumulative mortality in the back pain cohort could be explained by the higher comorbidity level in this group or by the association with more serious comorbidities (eg columnal bone metastases) than frozen shoulder.

We estimated a 22-year cumulative incidence of PD in the back pain cohort to be less than that in the frozen shoulder cohort; however, these results may have been impacted by the higher competing risk of death in the back pain cohort. Thus, the adjusted HRs comparing the frozen shoulder cohort to the back pain cohort were approximately 1 for the overall follow-up period.

Therefore, we cannot exclude detection bias, but we can extend our hypothesis to suggest that both frozen shoulder and back pain, and perhaps certain other musculoskeletal disorders, are early symptoms of parkinsonism and therefore increase the risk of clinical PD diagnosis. Additionally, if the detection of PD is associated with medical assessment in relation to frozen shoulder (or back pain), we would suspect detection bias affecting the estimates at short-term follow-up but less likely to affect long-term follow-up. Although the HRs for PD when comparing the frozen shoulder cohort to the general population cohort were highest at 0–1 years follow-up, the HRs remained above 1 even at the later follow-up periods of 6–10 years and 10–22 years, suggesting that detection bias cannot fully explain the association. This is also supported by higher HRs in the same follow-up period comparing the frozen shoulder to the back pain cohort. In the interpretation of the different follow-up periods, it is important to recognize that any start of follow-up postponed to later than the index date (eg, 1–22 years follow-up or 6–10 years follow-up) inherently represents a selected population of the original cohorts, as only those alive and PD free at the postponed start of follow-up would be included.

Furthermore, to address any detection bias caused by differences in comorbidity status and subsequent contact with medical providers, we performed an additional analysis adjusted for comorbidities, using the more extensive Charlson

comorbidity index. Had comorbidity status contributed to detection bias, we would expect adjusted HRs to be lower than unadjusted and would expect a further decrease in HRs when adjusting for additional comorbidities when comparing the frozen shoulder cohort with the general population cohort. However, the adjusted HRs were only slightly lower than the unadjusted HRs, and additional adjustment with the Charlson comorbidity index did not change the estimates.

Although our results indicate that frozen shoulder could be a pre-diagnostic manifestation of PD in some cases, we do not consider it a valuable screening tool. Even though frozen shoulder is rarer than back pain, results indicated that neither diagnosis has a high specificity for later development of PD. Additionally, the absolute risk of PD among patients with frozen shoulder was low, and the number needed to screen was correspondingly high. Thus, in the first year following frozen shoulder diagnosis, one would expect one additional PD diagnosis for every 3333 frozen shoulder patients compared with the general population. Therefore, the clinical impact of using frozen shoulder a predictive tool to identify unrecognized cases of PD is probably poor. However, delay in diagnosis and treatment of PD is still a concern; up to 50% of PD patients with previous frozen shoulder are referred to other specialists before a neurologist.[42]

Furthermore, delay in treatment of PD after first contact with a primary physician is associated with motor symptoms of limb and axial rigidity.[43] Among PD patients with a history of frozen shoulder, it was previously reported that initial symptoms suggestive of akinesia occurred twice as often as symptoms indicative of tremor.[21] In the light of this, our results and the high prevalence of frozen shoulder symptoms previously reported in patients with PD, we still find it important for physicians to consider the possibility of PD in patients with a history of frozen shoulder as well as back pain, and perhaps other musculoskeletal disorders, especially in the presence of PD suspect symptomatology.

## Methodological Considerations

Although the analyses were conducted in a large population-based frozen shoulder cohort, the number of outcomes were small in several stratified analyses, affecting the certainty of our estimates, as seen by the wide CIs.

Our study was limited to inpatient and outpatient hospital diagnoses of frozen shoulder, back pain, and PD. However, individuals with milder symptoms of frozen shoulder and back pain may have been diagnosed and treated in primary care settings and, therefore, not reported to the Danish medical registries. Not including data from primary care providers poses a risk of selection bias. Concerning PD, we must expect some misclassification, as the diagnosis of PD may be delayed when symptoms are mild. However, the absence of data from the Danish primary care system probably did not contribute to further misclassification in this study, as the diagnosis and treatment of PD is considered a specialist's task and occurs exclusively in hospital settings or specialist outpatient clinics.

The results of this study are best generalized to populations in which the available healthcare system has a similar approach to the diagnosis and treatment of frozen shoulder, back pain, and PD.

# Conclusion

In conclusion, we found an association between frozen shoulder diagnosis and an increased risk of receiving a PD diagnosis compared with the general population. Frozen shoulder may represent early manifestations of PD before cardinal motor symptoms are recognized, the increased risk persists for up to 22 years. Although, the absolute risk of PD and presumably the population-attributable risk are too low to recommend routine screening for PD in patients with frozen shoulder, it remains important for physicians to consider the possibility of PD, especially in the presence of PD suspect symptomatology.

# Abbreviations

PD, Parkinson's disease; DNPR, The Danish National Patient Registry; DCRS, The Danish Civil Registration System; ICD-8, The International Classification of Disease 8th Edition; ICD-10, The International Classification of Disease 10th edition; PYRs, Person years; HR, Hazard ratio; CI, Confidence interval.

# Data Sharing Statement

To protect the privacy of patients, it is by Danish law prohibited to make individual-level data publicly available.

## Ethics

Patient consent is not required by Danish law for studies based on routine electronic data. The study was reported to the Danish Data Protection Agency through registration at Aarhus University (record number: AU-2016-051-000001, sequential number 818).

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

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