ORIGINAL RESEARCH

Risk of Parkinson Disease and Secondary Parkinsonism in Myocardial Infarction Survivors

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BACKGROUND: In addition to primary neurodegenerative processes, vascular disorders, such as stroke, can lead to parkinsonism. However, some cardiovascular risk factors, such as smoking and elevated cholesterol levels, are associated with reduced risk of Parkinson disease. We examined the risk of Parkinson disease and secondary parkinsonism in 1-year survivors of myocardial infarction (MI).

METHODS AND RESULTS: We conducted a nationwide population-based matched cohort study using Danish medical registries from 1995 to 2016. We identified all patients with a first-time MI diagnosis and sampled a sex-, age-, and calendar year–matched general population comparison cohort without MI. Cox regression analysis was used to compute adjusted hazard ratios (aHRs) for Parkinson disease and secondary parkinsonism, controlled for matching factors and adjusted for relevant comorbidities and socioeconomic factors. We identified 181,994 patients with MI and 909,970 matched comparison cohort members (median age, 71 years; 62% men). After 21 years of follow-up, the cumulative incidence was 0.9% for Parkinson disease and 0.1% for secondary parkinsonism in the MI cohort. Compared with the general population cohort, MI was associated with a decreased risk of Parkinson disease (aHR, 0.80; 95% CI, 0.73–0.87) and secondary parkinsonism (aHR, 0.72; 95% CI, 0.54–0.94).

CONCLUSIONS: MI was associated with a 20% decreased risk of Parkinson disease and 28% decreased risk of secondary parkinsonism. Reduced risk may reflect an inverse relationship between cardiovascular risk factors and Parkinson disease.

Key Words: epidemiology ■ myocardial infarction ■ Parkinson disease

The number of myocardial infarction (MI) survivors has increased worldwide because of an ongoing demographic shift toward an elderly population combined with improved mortality rates following MI. In this growing population, the risk of neurovascular complications, such as ischemic stroke and vascular dementia, is markedly increased. Although the risk of cardiovascular disease is increased in patients with Parkinson disease, the risk of Parkinson disease in MI survivors remains unknown.

Parkinson disease is primarily a neurodegenerative disease, whereas parkinsonism has several underlying causes besides primary neurodegenerative processes, including a variety of vascular mechanisms. These may include lacunar infarcts and other vascular insults encompassing the substantia nigra, cerebral white matter, and other cerebral structures. Complications after MI, such as atrial fibrillation and regional wall motion abnormalities, may increase the risk of such infarcts. Likewise, heart failure and...
hypotension following MI may facilitate formation of watershed infarcts in susceptible areas of the brain.10 Cardiovascular drugs commonly initiated in the course of an MI (eg, verapamil and diltiazem) also are known to increase the risk of parkinsonism.11,12

Shared risk factors between MI and Parkinson disease include age and male sex, whereas coffee consumption and physical activity each are associated with a lower risk of both diseases.13 Conversely, several studies confirm that classic cardiovascular risk factors, such as smoking, hypercholesterolemia, increased blood pressure, and diabetes, are negatively associated with the risk of Parkinson disease.14-16 However, it is not known whether this inverse relationship extends to manifest atherosclerotic disease. As the underlying cause of Parkinson disease is largely unknown, identification of potential risk factors would contribute to our understanding of the disease. We therefore examined the long-term risk of Parkinson disease and secondary parkinsonism following first-time MI and the impact of common MI treatments and complications.

CLINICAL PERSPECTIVE

What Is New?
• In addition to primary neurodegenerative processes, cerebrovascular disorders can lead to parkinsonism.
• Although the risk of cardiovascular disease is increased in patients with Parkinson disease, the risk of Parkinson disease in myocardial infarction survivors remains unknown.
• In our study, myocardial infarction was associated with a 20% decreased risk of Parkinson disease and a 28% decreased risk of secondary parkinsonism compared with the general population.

What Are the Clinical Implications?
• Our observations suggest that myocardial infarction is negatively associated with Parkinson disease.
• This finding may reflect inverse associations between classic cardiovascular risk factors, such as smoking and elevated cholesterol, and Parkinson disease.
• The risk of Parkinson disease need not be a focus area during follow-up of patients with myocardial infarction.

METHODS

Setting and Design
The data that support the findings of this study are available from the corresponding author on reasonable request.

We conducted this nationwide population-based cohort study in Denmark, which had a cumulative population of 8 262 736 inhabitants during the study period (January 1, 1995, to December 31, 2016).17 The Danish National Health Service provides tax-supported health care, with free and equal access to general practitioners and hospitals for all Danish inhabitants. Accurate linkage of all registries at the individual level is possible in Denmark because of the unique central personal registry number assigned to each Danish citizen at birth and to residents on immigration.18

Patients With MI
We used the Danish National Patient Registry (DNPR) to identify all patients with a first-time inpatient diagnosis of MI during the study period. The DNPR has recorded information on all admissions to Danish nonpsychiatric hospitals since 1977 and on emergency department and outpatient clinic visits since 1995.19 Each hospital discharge or outpatient visit is recorded in the DNPR with one primary diagnosis and one or more secondary diagnoses classified according to the International Classification of Diseases, Eighth Revision (ICD-8), through 1993 and International Classification of Diseases, Tenth Revision (ICD-10), thereafter.19 We identified patients with MI using both primary and secondary diagnoses.

General Population Comparison Cohort
We created a general population comparison cohort using the Danish Civil Registration System, which has provided daily updates on vital statistics, including dates of birth, emigration, and death, since 1968.18 For each patient in the MI cohort, 5 individuals from the general population without an MI diagnosis were randomly selected and matched on sex, age, and calendar year of MI diagnosis.20 Each hospital discharge or outpatient visit is recorded in the DNPR with one primary diagnosis and one or more secondary diagnoses classified according to the International Classification of Diseases, Eighth Revision (ICD-8), through 1993 and International Classification of Diseases, Tenth Revision (ICD-10), thereafter.19 We identified patients with MI using both primary and secondary diagnoses.
Parkinson Disease and Secondary Parkinsonism

Data on inpatient and outpatient Parkinson disease and secondary parkinsonism diagnoses were retrieved from the DNPR.19 We also included secondary parkinsonism to consider patients with parkinsonism attributable to, for example, cerebrovascular insults following MI. In the DNPR, diagnoses are available for hospital admissions since 1977 and for outpatient clinic visits since 1995.19 We identified Parkinson disease and secondary parkinsonism using both primary and secondary diagnoses. The validity of Parkinson disease in the DNPR is high at 91%.21

Covariables

All patients’ medical histories were available in the DNPR since 197719 and the Danish Psychiatric Central Research Register since 1995.22 We obtained information on comorbidities that may represent confounders or shared risk factors for MI and parkinsonism. These consisted of all hospital inpatient and outpatient diagnoses of heart failure, angina pectoris, atrial fibrillation/atrial flutter, heart valve disease, hypercholesterolemia, hypertension, stroke, intermittent claudication, obesity, diabetes, chronic pulmonary disease (as an indicator of chronic smoking), alcoholism-related diseases, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, and a modified Charlson Comorbidity Index (CCI) score (excluding congestive heart failure, MI, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, and diabetes from the index). We also obtained information on personal gross income, employment status during the year preceding the index date, and highest education achieved from the Integrated Database for Labour Market Research.23

Finally, we included certain antipsychotics (specifically piperazine side chain neuroleptics) and calcium channel blockers from the nationwide prescription registry,24 as they are known to cause extrapyramidal adverse effects mimicking Parkinson disease11,25 and are commonly used in patients with cardiovascular disease.26,27

Surgical Procedures

We obtained information on coronary artery bypass graft surgery, percutaneous coronary intervention, and pacemaker implantation from the DNPR, which has coded surgery according to the Danish Classification of Surgical Procedures and Therapies until January 1, 1996, and according to the NOMESCO Classification of Surgical Procedures thereafter.19

Statistical Analysis

We characterized the MI and general population comparison cohorts according to sex, age groups (<60, 60–69, 70–79, and ≥80 years), index year calendar periods (1995–1999, 2000–2004, 2005–2009, and 2010–2016), comorbidities, and socioeconomic factors at baseline and at 1 year after MI. We followed up all patients with MI and members of the general population comparison cohort until the occurrence of any Parkinson disease or secondary parkinsonism diagnosis, emigration, death, or December 31, 2016, whichever came first. A priori, we disregarded the first year after MI and initiated follow-up thereafter, because parkinsonism diagnosed shortly after admission for MI is unlikely to be a consequence of MI and is prone to diagnostic bias shortly after MI. The Figure provides a flowchart of exclusions within the first year of MI and the resulting final study population.

We used cumulative incidence functions with death as a competing risk to calculate risks of Parkinson disease or secondary parkinsonism during 1 to 22 years of follow-up. This implies a maximum follow-up of 21 years. Using multivariable stratified Cox proportional hazards regression, we computed adjusted hazard ratios (aHRs) with 95% CIs, comparing patients with MI with members of the general population comparison cohort.28 The aHRs were controlled for sex, age, and calendar year by the matched study design and in multivariable analyses adjusted for preadmission diagnoses of heart failure, stable angina pectoris, atrial fibrillation or atrial flutter, valvular heart disease, hypercholesterolemia, hypertension, stroke, intermittent claudication, obesity, diabetes, chronic pulmonary disease, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified CCI score, antipsychotics, calcium channel blockers, and socioeconomic factors (income and employment). The proportional-hazards assumption was assessed graphically using log-log plots, and there were indications of violation within the total follow-up period. Therefore, we repeated all analyses using the Poisson regression approach,29 which does not require proportionality of hazards. We found no difference in the estimates with these 2 approaches and therefore report results from the Cox regression analyses. All codes used in the study are provided in Tables S1 and S2.

Additional Analyses

To identify clinical pathways with a potential impact on the association between MI and Parkinson disease or secondary parkinsonism, we stratified by cardiac procedures performed during hospital admission for MI.
and by complications occurring between MI and start of follow-up 1 year later.

The presence of potential interactions was examined in strata of sex, age groups, underlying preadmission comorbidity, different levels of comorbidity measured using modified CCI scores, and socioeconomic factors, the matching was dissolved and ahIRs were additionally adjusted for matching variables. Dissolving the matching introduced a lack of independence among members of the comparison cohort because they were matched with replacement. However, we did not use a robust variance estimator in the Cox regression analyses, because we did not detect any notable difference in doing so (the maximum difference was 0.01 in the CI) and because all estimates were tested with a Poisson regression model using a robust variance estimator, also with no difference compared with the original estimates.

**Sensitivity Analyses**

We performed several sensitivity analyses. First, given an assumed latency period for development of clinically overt parkinsonism following MI, we repeated the analyses sequentially excluding the initial 2, 3, and 5 years of follow-up. Second, we additionally adjusted for education, which was not included in the main analysis because data were unavailable for ≈18% of participants and because there was a strong collinearity with the other socioeconomic factors (income and employment). Third, we divided follow-up time into periods of 1 to 5 years, 6 to 10 years, 11 to 15 years, and 16 years to end of follow-up to examine whether associations changed over time. Fourth, we continued follow-up for members of the comparison cohort who experienced an MI during follow-up. Fifth, in a sensitivity analysis, we also calculated E-values for main estimates and the corresponding upper limit of the 95% CI. This allowed us to assess how strongly a single unmeasured binary confounder would need to be associated with both the exposure (MI) and outcome (Parkinson disease/secondary parkinsonism) to fully explain away the observed exposure-outcome association.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency (record number 1-16-02-268-14). According to Danish legislation, no approval from an ethics committee or informed consent from patients is required for registry-based studies in Denmark.

**RESULTS**

The study included 181,994 patients in the MI cohort and 909,970 individuals in the matched general
population comparison cohort. Median age at MI diagnosis was 71 (interquartile range, 60–80) years, and 62% of the study population were men. Median follow-up time was 4.1 (25th–75th percentile, 0.7–9.6) years for patients with MI and 6.6 (25th–75th percentile, 2.9–11.6) years for members of the comparison cohort. The difference in follow-up time arose mainly from the competing risk of death after MI. The MI cohort had an expected higher prevalence of cardiovascular conditions and CCI levels. Patients in the MI cohort had slightly lower income and educational levels, and a larger proportion were unemployed compared with the general population comparison cohort (Table 1). Findings were similar in MI survivors and members of the comparison cohort at 1 year after MI (Table S3).

### Table 1. Continued

| Characteristics | MI cohort (n=181,994) | Comparison cohort (n=909,970) |
|-----------------|-----------------------|------------------------------|
| **Men**         |                       |                              |
| Age, y          |                       |                              |
| <60             | 43,829 (24.1)         | 219,145 (24.1)               |
| 60–69           | 41,579 (22.8)         | 207,895 (22.8)               |
| 70–79           | 48,668 (26.7)         | 243,340 (26.7)               |
| ≥80             | 47,918 (26.3)         | 239,590 (26.3)               |
| **Median (25th–75th percentile)** | 71.0 (60–80) | 71.0 (60–80) |
| **Decade of diagnosis/index year** |                     |                              |
| 1995–1999       | 41,201 (22.6)         | 206,005 (22.6)               |
| 2000–2004       | 46,685 (25.7)         | 233,425 (25.7)               |
| 2005–2009       | 40,965 (22.5)         | 204,825 (22.5)               |
| 2010–2016       | 53,143 (29.2)         | 265,715 (29.2)               |
| **Comorbidity** |                       |                              |
| Heart failure   | 14,059 (7.7)          | 31,218 (3.4)                 |
| Angina pectoris | 29,771 (16.4)         | 59,753 (6.6)                 |
| Atrial fibrillation or flutter | 14,558 (8.0) | 53,802 (5.9) |
| Valvular heart disease | 7,265 (4.0) | 17,522 (1.9) |
| Hypercholesterolemia | 9,888 (5.4) | 24,847 (2.7) |
| Hypertension    | 63,119 (34.7)         | 216,747 (23.8)               |
| Stroke          | 14,062 (7.7)          | 45,301 (5.0)                 |
| Intermittent claudication | 5,426 (3.0) | 9445 (1.0) |
| Obesity         | 72,193 (4.0)          | 18,799 (2.1)                 |
| Diabetes        | 25,853 (14.2)         | 69,485 (7.6)                 |
| Chronic pulmonary disease | 18,988 (10.4) | 58,456 (6.4) |
| Alcoholism-related diseases | 5,975 (3.3) | 22,344 (2.5) |
| Head trauma     | 12,291 (6.8)          | 55,411 (6.1)                 |
| Osteoarthritis  | 23,633 (13.0)         | 104,967 (11.5)               |
| Anemia          | 9,588 (5.3)           | 29,929 (3.3)                 |
| Chronic kidney disease | 6,650 (3.7) | 12,044 (1.3) |
| Depression      | 6,244 (3.4)           | 24,152 (2.7)                 |
| **Drugs frequently associated with parkinsonism** |                     |                              |
| Typical antipsychotics (piperazine side chain neuroleptics) | 3,437 (1.9) | 14,288 (1.6) |
| Calcium channel blockers | 56,081 (30.8) | 184,974 (20.3) |
| **Modified CCI score*** |                     |                              |
| Normal          | 132,575 (72.8)        | 724,979 (79.6)               |
| Moderate        | 25,091 (13.8)         | 81,607 (9.0)                 |
| Severe          | 17,008 (9.3)          | 78,669 (8.6)                 |
| Very severe     | 7,320 (4.0)           | 25,097 (2.8)                 |
| **Income**      |                       |                              |
| Low             | 55,289 (30.4)         | 242,797 (26.7)               |
| Intermediate    | 53,763 (29.5)         | 250,765 (27.8)               |

*Categories of comorbidity were based on modified CCI scores: 0 (normal), 1 (moderate), 2 (severe), and ≥3 (very severe).

**Risk of Parkinson Disease and Secondary Parkinsonism**

During follow-up, 668 patients in the MI cohort were diagnosed with Parkinson disease and 71 with secondary parkinsonism. The cumulative incidence in the MI cohort after 21 years of follow-up was 0.9% for Parkinson disease and 0.1% for secondary parkinsonism. As a result of the competing risk of death, the cumulative incidence of Parkinson disease and secondary parkinsonism was higher in the general population comparison cohort than in the MI cohort (Table 2). MI was associated with a moderately decreased risk of both Parkinson disease (aHR, 0.80; 95% CI, 0.70–0.92) and secondary parkinsonism (aHR, 0.59; 95% CI, 0.40–0.87) compared with the general population comparison cohort.
Additional Analyses
In analyses stratified by procedures and complications (including stroke) after MI, we observed no impact on the risk of Parkinson disease or secondary parkinsonism (Table 3). In age-stratified analyses, the decreased risk of Parkinson disease was more pronounced for older age groups, whereas estimates were too imprecise to draw firm conclusion for secondary parkinsonism. We observed no sex differences (Table S4). Apart from a null association for patients with atrial fibrillation or flutter, alcoholism-related disease, and chronic kidney disease, the results remained largely unchanged in subgroup analyses of cardiac and noncardiac comorbidity, CCI levels, and use of drugs associated with extrapyramidal adverse effects mimicking Parkinson disease (Table S5). We observed no temporal difference in the association observed during early versus late time periods, apart from a weakened association from 2005 to 2009 for Parkinson disease (Table S6). In analyses stratified by primary versus secondary diagnoses of MI, the results also remained unchanged (Table S6). Across levels of income, employment status, and education, the results agreed with those of the main analysis, apart from a near null association for employed patients with MI (Table S7). Despite no apparent statistical significance at the 95% level of confidence in these additional analyses, we cannot entirely rule out type 1 errors attributable to limited sample sizes in these subgroup analyses.

Sensitivity Analyses
Results of the sensitivity analyses are presented in Table S8. The results were essentially unchanged when we sequentially excluded the initial 2, 3, and 5 years of follow-up. The results also remained robust when the model was extended to adjust for education, and when the 4 follow-up periods (1–5 years, 6–10 years, 11–15 years, and 16 years–end of follow-up) were considered separately. In addition, type of MI (ST-segment–elevation MI/non–ST-segment–elevation MI) did not substantially affect the results, although results were less precise in these MI subgroups. Finally, results were consistent when we continued follow-up for members of the population comparison cohort who experienced MI during follow-up (data not shown). The derived E-values were relatively large (E-values of 1.56 for Parkinson disease and 1.32 for secondary parkinsonism) in comparison with their main estimate counterparts (aHRs of 0.80 for Parkinson disease and 0.72 for secondary parkinsonism) (Figure S1). These results indicate that an unmeasured confounder would need to be strongly associated with both MI and Parkinson disease to fully explain our findings but still leave the potential for a single confounder with a moderate or large effect (eg, smoking) to explain away the observed association.

DISCUSSION
In this nationwide matched population-based cohort study with virtually complete follow-up of 181 994 MI survivors for 21 years, we found a moderately lower risk of both Parkinson disease and secondary parkinsonism compared with the general population. Apart from a null association in patients with MI who were employed or had specific comorbidity (atrial fibrillation or flutter, alcoholism-related disease, and chronic kidney disease), our results for Parkinson disease remained unchanged across subgroup and sensitivity analyses. For secondary parkinsonism, subgroups analyses were hampered by imprecise estimates attributable
to smaller sample sizes, and should be interpreted with caution. Our study is the first to examine the MI–Parkinson disease association, and from a clinical perspective our findings do not suggest the need for increased attention to development of Parkinson disease among MI survivors. Reduced risk of Parkinson disease and secondary parkinsonism after MI might be related to an inverse association with cardiovascular risk factors, such as smoking and blood cholesterol.

Although studies of the relation between classic cardiovascular risk factors and Parkinson disease have been inconsistent, most studies point to smoking as negatively associated with Parkinson disease.\textsuperscript{14,15,33–35} Our finding of a lower risk of Parkinson disease and secondary parkinsonism in MI survivors may partially be driven by a higher prevalence of smoking in MI survivors compared with the general population, although we adjusted for chronic pulmonary disease as a proxy for chronic smoking exposure. High blood levels of cholesterol also have been negatively associated with risk of Parkinson disease. A prospective study from the Netherlands reported high serum cholesterol levels to be associated with a decreased risk of Parkinson disease after adjusting for other cardiovascular risk factors (HR, 0.77; 95% CI, 0.64–0.94).\textsuperscript{36} This finding has been confirmed in a case-control study\textsuperscript{14} and a population-based cohort study.\textsuperscript{16} Although we adjusted for hypercholesterolemia diagnoses, the prevalence in the MI cohort is only 5.4% (Table 1). Hence, residual confounding of hypercholesterolemia may also partly drive our results of lower risk of Parkinson disease and secondary parkinsonism. High

### Table 3. Risk of Parkinson Disease and Secondary Parkinsonism in Patients With MI and Members of the General Population Cohort, by Procedures and Complications After MI

| Variable                                      | Parkinson disease | Secondary parkinsonism |
|-----------------------------------------------|-------------------|------------------------|
|                                               | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* |
| Procedures and complications during admission for MI |                   |                        |                          |                              |
| Coronary artery bypass grafting               |                   |                        |                          |                              |
| Yes                                           | 1.10 (0.69–1.69)  | 1.12 (0.61–2.05)       | …                        | …                            |
| No                                            | 0.85 (0.78–0.94)  | 0.79 (0.73–0.87)       | 0.09 (0.07–0.12)         | 0.74 (0.56–0.97)              |
| Percutaneous coronary intervention             |                   |                        |                          |                              |
| Yes                                           | 0.98 (0.80–1.20)  | 0.83 (0.71–0.98)       | 0.04 (0.02–0.08)         | 0.51 (0.26–0.99)              |
| No                                            | 0.80 (0.73–0.89)  | 0.78 (0.71–0.87)       | 0.10 (0.08–0.13)         | 0.78 (0.57–1.06)              |
| Pacemaker                                      |                   |                        |                          |                              |
| Yes                                           | 0.51 (0.21–1.06)  | 0.55 (0.23–1.34)       | …                        | …                            |
| No                                            | 0.86 (0.79–0.95)  | 0.80 (0.74–0.88)       | 0.09 (0.07–0.12)         | 0.74 (0.56–0.98)              |
| Complications during first year after MI      |                   |                        |                          |                              |
| Cardiogenic shock or pulmonary edema          |                   |                        |                          |                              |
| Yes                                           | 0.87 (0.62–1.20)  | 0.87 (0.60–1.27)       | 0.07 (0.03–0.15)         | 0.27 (0.07–0.96)              |
| No                                            | 0.86 (0.79–0.95)  | 0.79 (0.72–0.87)       | 0.09 (0.07–0.12)         | 0.77 (0.58–1.03)              |
| Stroke (ischemic or hemorrhagic)              |                   |                        |                          |                              |
| Yes                                           | 0.10 (0.01–0.56)  | 0.21 (0.02–2.49)       | 0.11 (0.01–0.60)         | …                            |
| No                                            | 0.87 (0.79–0.95)  | 0.80 (0.74–0.88)       | 0.09 (0.07–0.12)         | 0.71 (0.54–0.94)              |
| Heart failure                                 |                   |                        |                          |                              |
| Yes                                           | 0.73 (0.59–0.90)  | 0.88 (0.70–1.11)       | 0.09 (0.05–0.15)         | 0.72 (0.31–1.71)              |
| No                                            | 0.88 (0.80–0.97)  | 0.78 (0.71–0.86)       | 0.09 (0.07–0.12)         | 0.69 (0.51–0.93)              |
| Hypertension                                  |                   |                        |                          |                              |
| Yes                                           | 0.88 (0.76–1.01)  | 0.76 (0.68–0.86)       | 0.09 (0.06–0.12)         | 0.72 (0.49–1.06)              |
| No                                            | 0.85 (0.75–0.96)  | 0.85 (0.75–0.96)       | 0.09 (0.07–0.14)         | 0.72 (0.48–1.09)              |
| Atrial fibrillation or flutter                |                   |                        |                          |                              |
| Yes                                           | 0.91 (0.70–1.16)  | 1.01 (0.75–1.36)       | 0.19 (0.08–0.42)         | 0.78 (0.32–1.88)              |
| No                                            | 0.86 (0.78–0.94)  | 0.79 (0.72–0.86)       | 0.08 (0.06–0.11)         | 0.69 (0.51–0.93)              |

Ellipses (…) indicate insufficient data to compute a meaningful estimate. MI, myocardial infarction.

*Controlled for matching factors by study design and adjusted for heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, hypertension, stroke, intermittent claudication, obesity, diabetes, chronic pulmonary disease, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, antipsychotics, calcium channel blockers, income, and employment.
body mass index has been described as a risk factor for Parkinson disease in a Finnish observational study reporting a 2-fold increased risk for body mass index ≥30 kg/m²,37 whereas a recent Swedish population-based cohort study reported no association with Parkinson disease.38 This null association has further been supported in a case-control study29 and a population-based cohort study.15 High blood pressure has been both positively40 and negatively41,15 associated with the risk of Parkinson disease. It is interesting that stroke among MI survivors did not increase Parkinson disease risk in our study.

Several study strengths and limitations should be considered when interpreting our results. An important strength is the size of the study, allowing for examination of several possible interactions and mediators of the association between MI and parkinsonism, while retaining precision. The population-based design, within the setting of a tax-supported universal health care system with complete follow-up of all patients, largely eliminated selection biases.16 Registration of the MI diagnosis in the DNPR is accurate, with validation studies consistently reporting positive predictive values of >90% throughout the study period.19,30,41,42 The accuracy of Parkinson disease in the DNPR also is high at 91%.21 A concern is the unknown sensitivity of the diagnosis of Parkinson disease and secondary parkinsonism. The sensitivity may be higher in the MI cohort because of surveillance bias. However, this would lead to increased risk among patients with MI compared with the general population, which we did not observe. Despite extensive confounder adjustment for sex, age, comorbidity, and socioeconomic factors, our study is limited by its observational design. Thus, residual and unmeasured confounding cannot be ruled out and may partly underlie our results. More important, we lacked information on smoking and incompletely captured hypercholesterolemia, both of which are positively associated with MI43 and negatively associated with Parkinson disease.34,36

For the growing population of MI survivors and their managing physicians, the primary implication of our results is that the risk of Parkinson disease and parkinsonism is not increased compared with the general population. Conversely, our results point to a moderately decreased risk, which may reflect inverse associations between cardiovascular risk factors, such as smoking and elevated cholesterol, and Parkinson disease.

In conclusion, MI was associated with a moderately decreased risk of Parkinson disease and secondary parkinsonism, with robust results across subgroups and in sensitivity analyses.

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Dr Sørensen is the guarantor of this work, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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Disclosures
None.

Supplemental Material
Tables S1–S8
Figure S1

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SUPPLEMENTAL MATERIAL
**Table S1. Codes used in the study.**

| Disease                      | ICD-8 codes | ICD-10 codes | ATC code | Procedure codes |
|------------------------------|-------------|--------------|----------|-----------------|
| **Cardiovascular diseases**  |             |              |          |                 |
| Myocardial infarction        | 410         | I21          |          |                 |
| ST-segment myocardial infarction (STEMI) | N/A         | I211B, I210B, I213 |          |                 |
| Non-STEMI                    | N/A         | I211A, I210A, I214 |          |                 |
| Heart failure                | 427.09, 427.10, 427.11, 427.19, 428.99, 782.49 | I50, I11.0, I13.0, I13.2 |          |                 |
| Angina pectoris              | 413         | I20 (except I20.0), I25.1, I25.9 |          |                 |
| Atrial fibrillation or flutter | 427.93, 427.94 | I48          |          |                 |
| Valvular heart disease       | 394-398     | I05, I06, I07, I08.0, I09.8, I34-I37, I39.0, I39.3, I51.1A, Q22 |          |                 |
| Hypercholesterolemia         | 272.00      | E780         |          |                 |
| Hypertension                 | 400-404     | DI10-DI15, I67.4 |          | Combination treatment of at least two redeemed prescriptions for different types of the following classes of antihypertensive drugs within 180 days prior to myocardial infarction: α-adrenergic blockers, ATC: C02A, C02B, C02C, non-loop diuretics, ATC: C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52, vasodilators, ATC: C02DB, C02DD, C02DG, C04, C05, β-blockers, ATC: C07, calcium channel blockers, ATC: C07F, C08, C09BB, C09DB, and reninangiotensin system inhibitors, ATC: C09 |
| Stroke (ischemic and intracerebral) | 431, 433-434 | I61, I63-I64 |          |                 |
| Condition                                      | ICD-10 Code                |
|------------------------------------------------|----------------------------|
| Intermittent claudication                      | 443.89–443.99              |
| Cardiogenic shock and pulmonary edema          | 427.10, 427.11             |
| Non-cardiovascular diseases                    |                            |
| Obesity                                        | 277                        |
| Diabetes mellitus (excluding 249.02, 250.02)    | 249, 250                   |
| Chronic pulmonary disease                      | 490-493; 515-518           |
| Alcoholism-related diseases                    | 980, 291.09-291.99, 303.09-303.99, 571.09-571.11, 577.10 |
| Head trauma                                    | 800-803, 850-854           |
| Depression                                     | 296.09, 296.29, 298.09, 300.49 |
| Osteoarthritis                                 | 713                        |
| Anemia                                         | 280-281, 283-285           |
| Chronic kidney disease                         | 249.02, 250.02, 753.10-753.19, 582, 583, 584, 590.09, 593.20, 792 |
| Drug frequently causing parkinsonism           |                            |
| Typical antipsychotics (piperazine side chain neuroleptics) | N05AB                     |
| Calcium-channel blockers                       |                            |
| Outcomes                                       |                            |
| Parkinson’s disease                            | 342                        |
| Secondary parkinsonism                         | –                          |
| Procedures during admission                    |                            |
Coronary artery bypass graft surgery
Before 1996: 30009, 30019, 30029, 30039, 30049, 30059, 30069, 30079, 30089, 30099, 30109, 30119, 30120, 30129, 30139, 30149, 30159, 30169, 30179, 30189, 30199, 30200
After 1996: KFNA-E, KFNH20

Percutaneous coronary intervention
Before 1996: 30350, 30354, 30240
After 1996: KFNG, KFNF

Pacemaker
Before 1996: 30930, 32140, 32199, 32490
After 1996: BFCA
| Disease                          | Weight | ICD-8 | ICD-10 |
|---------------------------------|--------|-------|--------|
| Peripheral vascular disease     | 1      | 440, 441, 442, 443, 444, 445 | 170, 171, 172, 173, 174, 177 |
| Cerebrovascular disease         |        | 430-438; 160-169, G45, G46 | |
| Dementia                        |        | 290.09-290.19, 293.09; F00-F03, F05.1, G30 | |
| Connective tissue disease       |        | 712, 716, 734, 446, 135.99; M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86 | |
| Ulcer disease                   |        | 530.91, 530.98, 531-534; K22.1, K25-K28 | |
| Mild liver disease              |        | 571, 57301, 57304; B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0 | |
| Hemiplegia                      | 2      | 344; G81, G82 | |
| Non-metastatic solid tumor      |        | 140-194; C00-C75 | |
| Leukemia                        |        | 204-207; C91-C95 | |
| Lymphoma                        |        | 200-203, 275.59; C81-C85, C88, C90, C96 | |
| Moderate to severe liver disease| 3      | 070.00, 070.02, 070.04, 070.06, 070.08, 070.09, 573.00, 456.00-456.09; B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85 | |
| Metastatic cancer               | 6      | 195-198, 199; C76-C80 | |
| AIDS                            |        | 079.83; B21-B24 | |
Table S3. Characteristics of myocardial infarction survivors and members of the general population comparison cohort at 1 year after myocardial infarction, Denmark, 1995-2012.

| Characteristics                        | Myocardial infarction cohort (n=131,396) | Comparison cohort (n=630,166) |
|----------------------------------------|------------------------------------------|------------------------------|
| Male                                   | 84,818 (64.6)                            | 408,024 (64.7)               |
| Age, years                             |                                          |                              |
| <60                                    | 39,027 (29.7)                            | 193,419 (30.7)               |
| 60–69                                  | 34,235 (26.1)                            | 167,756 (26.6)               |
| 70–79                                  | 33,882 (25.8)                            | 161,726 (25.7)               |
| ≥80                                    | 24,252 (18.5)                            | 107,265 (17.0)               |
| Median (25th–75th percentile)          | 67 (57–77)                               | 67 (57–76)                   |
| Decade of diagnosis / index date       |                                          |                              |
| 1996–1999                              | 28,448 (21.7)                            | 136,107 (21.6)               |
| 2000–2004                              | 34,128 (26.0)                            | 162,980 (25.9)               |
| 2005–2009                              | 31,361 (23.9)                            | 150,336 (23.9)               |
| 2010–2016                              | 37,459 (28.5)                            | 180,743 (28.7)               |
| Comorbidity                            |                                          |                              |
| Heart failure                          | 28,317 (21.6)                            | 18,318 (2.9)                 |
| Angina pectoris                        | 77,330 (58.9)                            | 39,782 (6.3)                 |
| Atrial fibrillation or flutter         | 17,524 (13.3)                            | 34,016 (5.4)                 |
| Valvular heart disease                 | 8,068 (6.1)                              | 11,615 (1.8)                 |
| Hypercholesterolemia                   | 35,356 (26.9)                            | 18,976 (3.0)                 |
| Hypertension                           | 81,433 (62.0)                            | 150,163 (23.8)               |
| Stroke                                 | 10,826 (8.2)                             | 29,127 (4.6)                 |
| Intermittent claudication              | 4,996 (3.8)                              | 6,607 (1.0)                  |
| Obesity                                | 8,012 (6.1)                              | 13,978 (2.2)                 |
| Diabetes mellitus                      | 21,264 (16.2)                            | 48,656 (7.7)                 |
| Chronic pulmonary disease              | 16,160 (12.3)                            | 39,467 (6.3)                 |
| Alcoholism-related diseases            | 4,562 (3.5)                              | 17,411 (2.8)                 |
| Head trauma                            | 9,537 (7.3)                              | 40,078 (6.4)                 |
| Osteoarthritis                         | 17,269 (13.1)                            | 70,382 (11.2)                |
| Anemia                                 | 9,540 (7.3)                              | 18,389 (2.9)                 |
| Chronic kidney disease                 | 5,828 (4.4)                              | 8,196 (1.3)                  |
| Depression                             | 5,111 (3.9)                              | 16,321 (2.6)                 |
| Drugs frequently causing parkinsonism  |                                          |                              |
| Typical antipsychotics (piperazine side chain neuroleptics) | 2,308 (1.8) | 9,115 (1.4) |
| Calcium-channel blockers               | 53,126 (40.4)                            | 127,167 (20.2)               |
| Modified CCl score*                   |                                          |                              |
| Normal                                 | 94,456 (71.9)                            | 509,388 (80.8)               |
| Moderate                               | 19,848 (15.1)                            | 52,884 (8.4)                 |
| Severe                                 | 11,860 (9.0)                             | 51,338 (8.1)                 |
| Very severe                            | 5,232 (4.0)                              | 16,556 (2.6)                 |
| Income                                 |                                          |                              |
| Low                                    | 39,983 (30.4)                            | 165,356 (26.2)               |
| Intermediate                           | 37,309 (28.4)                            | 163,355 (25.9)               |
| High                                   | 30,093 (22.9)                            | 147,668 (23.4)               |
| Very high                              | 23,971 (18.2)                            | 153,272 (24.3)               |
| Missing                                | 40 (0.0)                                 | 515 (0.1)                    |
| Employment                             |                                          |                              |
| Employed                               | 40,956 (31.2)                            | 231,073 (36.7)               |
| Early retirement                       | 19,346 (14.7)                            | 75,547 (12.0)                |
| Unemployed                             | 4,100 (3.1)                              | 15,501 (2.5)                 |
| State pensioner                        | 66,756 (50.8)                            | 305,731 (48.5)               |
| Missing                                | 238 (0.2)                                | 2,314 (0.4)                  |
| Education                              |                                          |                              |
| Basic education or primary school      | 53,463 (40.7)                            | 222,997 (35.4)               |
| Youth education, high school, or similar education | 44,197 (33.6) | 219,647 (34.9) |
| Higher education                       | 16,608 (12.6)                            | 114,198 (18.1)               |
| Unknown                                | 17,128 (13.0)                            | 73,324 (11.6)                |

Table values are given as n (%). CCI indicates Charlson Comorbidity Index.

*Categories of comorbidity were based on modified Charlson Comorbidity Index scores: 0 (normal), 1 (moderate), 2 (severe), and ≥3 (very severe).
Table S4. Risk of parkinsonism following myocardial infarction compared with the general population cohort, by sex and age.

| Characteristics | Parkinson’s disease | Secondary parkinsonism |
|----------------|---------------------|------------------------|
|                | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* |
| Female         | 0.57 (0.47–0.68)     | 0.80 (0.68–0.95)       | 0.08 (0.05–0.13)        | 0.97 (0.57–1.68)       |
| Male           | 1.02 (0.92–1.14)     | 0.79 (0.72–0.88)       | 0.10 (0.07–0.13)        | 0.67 (0.48–0.93)       |
| <60 years      | 0.61 (0.47–0.79)     | 0.93 (0.73–1.19)       | 0.05 (0.03–0.10)        | 1.06 (0.41–2.73)       |
| 60-69 years    | 1.16 (0.99–1.37)     | 0.83 (0.71–0.97)       | 0.15 (0.10–0.22)        | 0.78 (0.49–1.22)       |
| 70-79 years    | 1.11 (0.98–1.25)     | 0.73 (0.64–0.84)       | 0.13 (0.08–0.19)        | 0.62 (0.39-0.98)       |
| 80+ years      | 0.48 (0.40–0.59)     | 0.76 (0.61–0.95)       | 0.03 (0.01–0.06)        | 0.46 (0.17–1.23)       |

CI indicates confidence interval.

*Controlled for matching factors by study design and adjusted for heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, antipsychotics, calcium channel blockers, income, and employment.
Table S5. Risk of Parkinson’s disease and parkinsonism following myocardial infarction compared with the general population cohort, by history of comorbidity.

| Comorbidity                        | Parkinson’s disease | Secondary parkinsonism |
|------------------------------------|---------------------|------------------------|
|                                    | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* |
| Heart failure                      |                     |                        |
| Yes                                | 0.50 (0.31–0.76)    | 0.65 (0.41–1.05)       | 0.04 (0.01–0.13) | 0.33 (0.07–1.48) |
| No                                 | 0.88 (0.80–0.97)    | 0.79 (0.73–0.86)       | 0.09 (0.07–0.12) | 0.74 (0.57–0.96) |
| Angina pectoris                    |                     |                        |
| Yes                                | 1.05 (0.82–1.32)    | 0.77 (0.62–0.95)       | 0.07 (0.04–0.13) | 0.64 (0.32–1.26) |
| No                                 | 0.84 (0.76–0.92)    | 0.79 (0.73–0.87)       | 0.09 (0.07–0.12) | 0.74 (0.57–0.98) |
| Atrial fibrillation or flutter     |                     |                        |
| Yes                                | 0.95 (0.70–1.27)    | 1.26 (0.92–1.73)       | 0.27 (0.08–0.72) | 1.46 (0.63–3.39) |
| No                                 | 0.86 (0.78–0.94)    | 0.79 (0.73–0.86)       | 0.09 (0.06–0.11) | 0.69 (0.53–0.90) |
| Valvular heart disease             |                     |                        |
| Yes                                | 0.43 (0.22–0.80)    | 0.58 (0.30–1.12)       | 0.08 (0.01–0.45) | 0.51 (0.05–5.10) |
| No                                 | 0.87 (0.79–0.95)    | 0.79 (0.73–0.86)       | 0.09 (0.07–0.12) | 0.72 (0.56–0.93) |
| Hypercholesterolemia               |                     |                        |
| Yes                                | 2.43 (0.86–5.45)    | 1.04 (0.69–1.58)       | 0.07 (0.02–0.17) | 1.57 (0.43–5.71) |
| No                                 | 0.84 (0.77–0.92)    | 0.78 (0.72–0.85)       | 0.09 (0.07–0.12) | 0.71 (0.55–0.92) |
| Hypertension                       |                     |                        |
| Yes                                | 0.89 (0.76–1.04)    | 0.88 (0.76–1.03)       | 0.10 (0.06–0.18) | 0.70 (0.44–1.11) |
| No                                 | 0.85 (0.76–0.95)    | 0.75 (0.68–0.83)       | 0.09 (0.07–0.12) | 0.73 (0.54–0.99) |
| Stroke                             |                     |                        |
| Yes                                | 0.61 (0.42–0.85)    | 0.78 (0.54–1.14)       | 0.14 (0.06–0.28) | 0.88 (0.38–2.06) |
| No                                 | 0.88 (0.80–0.96)    | 0.79 (0.73–0.86)       | 0.09 (0.07–0.12) | 0.71 (0.54–0.93) |
| Intermittent Claudication           |                     |                        |
| Yes                                | 0.22 (0.08–0.52)    | 0.48 (0.18–1.31)       | – | – |
| No                                 | 0.87 (0.80–0.96)    | 0.79 (0.73–0.86)       | 0.09 (0.07–0.12) | 0.73 (0.57–0.95) |
| Obesity                            |                     |                        |
| Yes                                | 0.51 (0.30–0.85)    | 0.72 (0.40–1.27)       | – | – |
| No                                 | 0.87 (0.79–0.95)    | 0.79 (0.73–0.86)       | 0.09 (0.07–0.12) | 0.76 (0.59–0.98) |
| Diabetes mellitus                  |                     |                        |
| Yes                                | 0.87 (0.65–1.14)    | 0.91 (0.70–1.18)       | 0.08 (0.04–0.17) | 0.38 (0.17–0.85) |
| No                                 | 0.86 (0.78–0.95)    | 0.78 (0.71–0.85)       | 0.09 (0.07–0.12) | 0.78 (0.60–1.01) |
| Chronic pulmonary disease          |                     |                        |
| Yes                                | 0.45 (0.31–0.63)    | 0.66 (0.45–0.96)       | 0.05 (0.02–0.13) | 0.57 (0.19–1.67) |
| No                                 | 0.90 (0.82–0.98)    | 0.80 (0.73–0.87)       | 0.10 (0.07–0.12) | 0.73 (0.57–0.95) |
| Alcoholism-related disease         |                     |                        |
| Yes                                | 0.68 (0.36–1.22)    | 0.98 (0.54–1.79)       | 0.28 (0.10–0.67) | 1.53 (0.53–4.45) |
| No                                 | 0.87 (0.79–0.95)    | 0.79 (0.72–0.86)       | 0.09 (0.07–0.11) | 0.69 (0.53–0.90) |
| Head trauma                        |                     |                        |
| Yes                                | 0.79 (0.51–1.19)    | 0.93 (0.64–1.37)       | 0.14 (0.04–0.38) | 0.81 (0.26–2.56) |
| No                                 | 0.87 (0.79–0.95)    | 0.78 (0.72–0.85)       | 0.09 (0.07–0.12) | 0.71 (0.55–0.93) |
| Osteoarthritis                     |                     |                        |
| Yes                                | 0.81 (0.63–1.04)    | 0.81 (0.63–1.04)       | 0.05 (0.02–0.12) | 0.40 (0.17–0.94) |
| No                                 | 0.87 (0.79–0.95)    | 0.79 (0.72–0.86)       | 0.10 (0.07–0.12) | 0.78 (0.60–1.02) |
|                      | Yes          | No            | Chronic kidney disease | Depression | Modified CCI score | Typical antipsychotics use within the first year after myocardial infarction | Calcium-channel blockers use within the first year after myocardial infarction |
|----------------------|--------------|---------------|------------------------|------------|-------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|                      | 0.44 (0.26–0.72) | 0.87 (0.80–0.96) | 0.74 (0.42–1.24) | 0.87 (0.79–0.95) | 0.86 (0.78–0.94) | 1.46 (0.61–3.02) | 0.93 (0.77–1.12) | 0.91 (0.82–1.00) | 0.51 (0.25–0.96) | 0.82 (0.47–1.43) | 0.79 (0.73–0.86) | 0.78 (0.72–0.85) | 0.80 (0.74–0.87) | 0.91 (0.87–1.78) | 0.91 (0.87–1.78) | 0.51 (0.25–0.96) |
|                      | 0.82 (0.47–1.43) | 0.79 (0.73–0.86) | 1.27 (0.67–2.39) | 0.78 (0.72–0.85) | 0.80 (0.74–0.87) | 0.54 (0.33–0.88) | 0.54 (0.33–0.88) | 0.79 (0.72–0.87) | 0.91 (0.47–1.78) | 0.06 (0.01–0.21) | 0.09 (0.02–0.32) | 0.09 (0.07–0.12) | 0.20 (0.07–0.45) | 0.06 (0.01–0.21) | 0.06 (0.01–0.21) |
|                      |              |               | 0.06 (0.01–0.21) | 0.09 (0.07–0.12) | 0.09 (0.07–0.12) | 0.28 (0.03–1.49) | 0.28 (0.03–1.49) | 0.09 (0.07–0.12) | 0.09 (0.07–0.12) | 0.71 (0.54–0.93) |                      |                      |                      |                      |                      |
|                      |              |               | 0.41 (0.09–1.86) | 0.74 (0.57–0.95)  | 0.74 (0.57–0.95) | –                     | –                     | 0.86 (0.79–0.94) | 0.82 (0.74–0.91) | 0.82 (0.74–0.91) | 0.82 (0.74–0.91) | 0.78 (0.72–0.85) | 0.79 (0.73–0.86) | 0.78 (0.72–0.85) | 0.78 (0.72–0.85) | 0.78 (0.72–0.85) |
|                      |              |               | 0.72 (0.26–2.01) | 0.72 (0.55–0.93)  | 0.71 (0.54–0.93) |                      |                      | 0.83 (0.75–0.92) | 0.83 (0.75–0.92) | 0.83 (0.75–0.92) | 0.83 (0.75–0.92) | 0.80 (0.74–0.87) | 0.78 (0.72–0.85) | 0.78 (0.72–0.85) | 0.78 (0.72–0.85) | 0.78 (0.72–0.85) |
|                      |              |               | 0.41 (0.09–1.86) | 0.74 (0.57–0.95)  | 0.74 (0.57–0.95) |                      |                      | 0.06 (0.01–0.21) | 0.06 (0.01–0.21) | 0.06 (0.01–0.21) | 0.06 (0.01–0.21) | 0.06 (0.01–0.21) | 0.06 (0.01–0.21) | 0.06 (0.01–0.21) | 0.06 (0.01–0.21) | 0.06 (0.01–0.21) |

– Indicates insufficient data to compute a meaningful estimate; CCI, Charlson Comorbidity Index, CI, confidence interval.

*Adjusted for age, sex, calendar year, heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, antipsychotics, calcium channel blockers, income, and employment (except the stratified variable).
Table S6. Risk of Parkinson’s disease and parkinsonism following myocardial infarction compared with the general population cohort, by calendar periods and type of myocardial infarction diagnosis.

| Year/diagnosis                  | Parkinson’s disease | Secondary parkinsonism |
|---------------------------------|---------------------|------------------------|
|                                 | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* |
| 1995–1999                       | 0.85 (0.75–0.97)    | 0.79 (0.68–0.92)       | 0.12 (0.08–0.16)    | 0.93 (0.59–1.47)       |
| 2000–2004                       | 0.72 (0.62–0.83)    | 0.75 (0.64–0.87)       | 0.08 (0.06–0.12)    | 0.77 (0.48–1.23)       |
| 2005–2009                       | 0.69 (0.58–0.82)    | 0.91 (0.77–1.09)       | 0.01 (0.01–0.04)    | 0.15 (0.05–0.43)       |
| 2010–2016                       | 0.26 (0.18–0.35)    | 0.75 (0.55–1.02)       | 0.03 (0.01–0.06)    | 0.31 (0.06–1.72)       |
| Primary diagnosis of myocardial infarction | 0.88 (0.80–0.97)    | 0.80 (0.73–0.87)       | 0.10 (0.07–0.12)    | 0.72 (0.54–0.95)       |
| Secondary diagnosis of myocardial infarction | 0.60 (0.44–0.82)    | 0.89 (0.63–1.24)       | 0.05 (0.02–0.12)    | 0.62 (0.11–3.45)       |

CI indicates confidence interval.

*Controlled for matching factors by study design and adjusted for heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, antipsychotics, calcium channel blockers, income, and employment.
Table S7. Risk of Parkinson’s disease and parkinsonism following myocardial infarction compared with the general population cohort, restricted to different socioeconomic status levels in both cohorts.

| Socioeconomic Characteristics | Parkinson’s disease | | | Secondary parkinsonism | | | |
|------------------------------|---------------------|-----------------|-----------------|---------------------|-----------------|-----------------|-----------------|
|                              | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* |
| **Income**                   |                     |                               |                               |                               |
| Low                          | 0.73 (0.63–0.85)    | 0.69 (0.59–0.81)              | 0.09 (0.06–0.13)              | 0.61 (0.39–0.95)              |
| Intermediate                 | 0.97 (0.82–1.14)    | 0.88 (0.76–1.02)              | 0.10 (0.06–0.15)              | 0.79 (0.50–1.25)              |
| High                         | 0.80 (0.67–0.97)    | 0.75 (0.63–0.89)              | 0.09 (0.05–0.15)              | 0.70 (0.41–1.18)              |
| Very high                    | 0.93 (0.74–1.16)    | 0.86 (0.71–1.04)              | 0.10 (0.05–0.20)              | 0.95 (0.49–1.87)              |
| Unknown                      | 2.73 (0.21–12.12)   | 2.17 (0.18–26.46)             | –                             | –                               |
| **Employment**               |                     |                               |                               |                               |
| Employed                     | 0.82 (0.68–0.98)    | 0.92 (0.78–1.08)              | 0.08 (0.05–0.14)              | 0.94 (0.55–1.59)              |
| Early retirement             | 1.10 (0.84–1.41)    | 0.84 (0.68–1.03)              | 0.13 (0.06–0.24)              | 0.74 (0.41–1.36)              |
| Unemployed                   | 0.76 (0.33–1.58)    | 0.80 (0.42–1.50)              | 0.13 (0.04–0.33)              | 2.72 (0.77–9.65)              |
| State pensioner              | 0.82 (0.74–0.91)    | 0.73 (0.66–0.82)              | 0.09 (0.06–0.12)              | 0.60 (0.42–0.84)              |
| Missing                      | 2.44 (0.56–6.98)    | 1.76 (0.50–6.23)              | –                             | –                               |
| **Education**                |                     |                               |                               |                               |
| Basic education, primary school | 0.82 (0.71–0.94)    | 0.78 (0.68–0.88)              | 0.09 (0.06–0.13)              | 0.74 (0.51–1.08)              |
| Youth education, high school or similar education | 1.01 (0.85–1.18) | 0.90 (0.78–1.03) | 0.13 (0.08–0.20) | 0.92 (0.61–1.40) |
| Higher education             | 1.12 (0.84–1.48)    | 0.74 (0.59–0.93)              | 0.09 (0.03–0.21)              | 0.54 (0.23–1.25)              |
| Unknown                      | 0.51 (0.40–0.64)    | 0.72 (0.57–0.92)              | 0.04 (0.02–0.08)              | 0.44 (0.19–1.02)              |

* Indicates insufficient data to compute a meaningful estimate; CI, confidence interval.

*Adjusted for age, sex, calendar year, heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, antipsychotics, calcium channel blockers, income, and employment (except the stratified variable).
Table S8. Sensitivity analyses of the association between myocardial infarction and risk of Parkinson’s disease and parkinsonism.

| Analysis change                                      | Parkinson’s disease | Secondary parkinsonism |
|------------------------------------------------------|---------------------|------------------------|
|                                                      | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* | Cumulative risk, % (95% CI) | Adjusted hazard ratio (95% CI)* |
| Excluding initial years of follow-up (years since diagnosis) |                     |                        |                          |                             |
| 2–22 years                                           | 0.87 (0.78–0.95)    | 0.81 (0.74–0.89)       | 0.09 (0.07–0.12)         | 0.73 (0.54–0.98)            |
| 3–22 years                                           | 0.85 (0.76–0.94)    | 0.81 (0.73–0.89)       | 0.09 (0.07–0.12)         | 0.75 (0.55–1.03)            |
| 5–22 years                                           | 0.82 (0.73–0.92)    | 0.82 (0.73–0.92)       | 0.10 (0.07–0.13)         | 0.91 (0.63–1.30)            |
| Additionally adjusting for education                | 0.86 (0.79–0.94)    | 0.80 (0.73–0.87)       | 0.09 (0.07–0.12)         | 0.72 (0.54–0.94)            |
| Disaggregating the follow-up                         |                     |                        |                          |                             |
| 1–5 years                                            | 0.22 (0.20–0.25)    | 0.76 (0.66–0.87)       | 0.02 (0.01–0.03)         | 0.51 (0.32–0.82)            |
| 6–10 years                                           | 0.33 (0.29–0.38)    | 0.81 (0.69–0.94)       | 0.04 (0.03–0.06)         | 0.75 (0.46–1.23)            |
| 11–15 years                                          | 0.41 (0.35–0.49)    | 0.92 (0.75–1.13)       | 0.05 (0.03–0.08)         | 1.35 (0.71–2.58)            |
| 16 years–22 years                                    | 0.33 (0.22–0.47)    | 0.68 (0.44–1.04)       | –                        | –                            |
| Type of myocardial infarction                        | 0.89 (0.74–1.06)    | 0.93 (0.79–1.09)       | 0.07 (0.04–0.13)         | 0.61 (0.33–1.14)            |

*– Indicates insufficient data to compute a meaningful estimate; CI, confidence interval; STEMI, ST-segment elevation myocardial infarction.

*Controlled for matching factors by study design and adjusted for heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, antipsychotics, calcium channel blockers, income, and employment.
**Figure S1.** Required strength of an unmeasured confounder for Parkinson’s disease (upper panel) and secondary parkinsonism (lower panel) to fully explain the main estimate counterpart. The graphs illustrate how strongly an unmeasured confounder would need to be associated with myocardial infarction (prevalence ratio for exposure–confounder association [PR_{EC}]) and Parkinson’s disease or secondary parkinsonism (relative risk of the disease in patients with the confounder [RR_{CD}]) to fully explain away our estimates. The graphs depict the adjusted hazard ratio for the outcomes along with the upper limit of the 95% confidence interval (CI).