Estrogen-related and other disease diagnoses preceding Parkinson’s disease

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Purpose: Estrogen exposure has been associated with the occurrence of Parkinson’s disease (PD), as well as many other disorders, and yet the mechanisms underlying these relations are often unknown. While it is likely that estrogen exposure modifies the risk of various diseases through many different mechanisms, some estrogen-related disease processes might work in similar manners and result in association between the diseases. Indeed, the association between diseases need not be due only to estrogen-related factors, but due to similar disease processes from a variety of mechanisms.

Patients and methods: All female Parkinson’s disease cases between 1982 and 2007 (n = 12,093) were identified from the Danish National Registry of Patients, along with 10 controls matched by years of birth and enrollment. Conditional logistic regressions (CLR) were used to calculate risk of PD after diagnosis of the estrogen-related diseases, endometriosis and osteoporosis, conditioning on years of birth and enrollment. To identify novel associations between PD and any other preceding conditions, CLR was also used to calculate the odds ratios (ORs) for risk of PD for 202 different categories of preceding disease diagnoses. Empirical Bayes methods were used to identify the robust associations from the over 200 associations produced by this analysis.

Results: We found a positive association between osteoporosis and osteoporotic fractures and PD (OR = 1.18, 95% confidence interval [CI] of 1.08–1.28), while a lack of association was observed between endometriosis and PD (OR = 1.37, 95% CI 0.99–1.90). Using empirical Bayes analyses, 24 additional categories of diseases, likely unrelated to estrogen exposure, were also identified as potentially associated with PD.

Conclusion: We identified several novel associations, which may provide insight into common causal mechanisms between the diseases or greater understanding of potential early preclinical signs of PD. In particular, the associations with several categories of mental disorders suggest that these may be early warning signs of PD onset or these diseases (or the causes of these diseases) may predispose to PD.

Keywords: Parkinson’s disease, estrogen, osteoporosis, endometriosis, empirical bayes

Introduction
Parkinson’s disease (PD) is a degenerative movement disorder that causes debilitating symptoms of tremor, rigidity, and bradykinesia usually occurring late in life. Sex is a consistently observed, but as of yet unexplained, risk factor for Parkinson’s disease. Women are two-thirds as likely as age-matched men to develop Parkinson’s disease.1 This decreased risk of PD in women, compared with men, has led to research into potential neuro-protective effects of estrogen on PD risk and treatment in particular. Improved motor function has been associated with estrogen treatment in studies...
of women with PD. Furthermore, studies have shown some, although not all, factors associated with estrogen, such as hormone replacement therapy, length of fertile life, or receipt of hysterectomy are associated with PD risk. However, other studies have shown no, or an inverse association, to the same or similar factors.

Estrogen exposure can not only be linked to Parkinson’s disease, but other diseases as well; both as a potential risk factors or protective factors. As with Parkinson’s disease, the underlying mechanism behind these relations is often unknown. Under the simplest scenarios, it could be expected that diseases associated with greater estrogen exposure would be associated with a lower risk of PD and vice versa. In reality, estrogen exposure probably modifies the risk of various diseases through different mechanisms and interactions with other susceptibility factors. Nevertheless, some estrogen-related disease processes may work in similar manners, resulting in an association between the diseases.

### Diseases related to increased estrogen exposure

Diseases such as breast cancer, endometrial cancer, and endometriosis are associated with increased cumulative exposure to estrogen. We might expect to see a decreased incidence of PD in women suffering from these diseases, if the mechanisms through which estrogen modulates risk in any of those diseases are similar to the mechanisms in PD. Both breast and endometrial cancers have been examined as precedent conditions in case-control studies of PD, and no association has been found; however, many studies have reported overall reduced cancer rates or mortality in PD patients. These reports suggest a pathogenic link between PD and cancer that may supersede any estrogen-related factors. There have not, however, been any studies of the mechanisms through which estrogen modulates risk in diseases related to increased estrogen exposure.

### Diseases related to decreased estrogen exposure

Osteoporosis is also associated with estrogen; reduced cumulative exposure to estrogen increases the risk of osteoporosis. Osteoporosis has been studied in patients with PD, partially because of the increased likelihood of falls in PD patients that lead to fractures. While the characteristic symptoms of postural instability in PD patients may explain the increased risk of fracture, lower bone mineral density (BMD) has also been observed in PD patients compared with age and sex matched controls, particularly in women. Suggested explanations for this difference include lower BMI, reduced exposure to sunlight, and lower vitamin D levels in people suffering from PD. Smoking, while related to both diseases, is a less likely explanation for the relationship as it may be associated with increased risk of osteoporosis as compared with an association to decreased risk of PD. It is also possible the association is due to a common estrogen related mechanism, increasing the risk of both diseases.

### Novel associations

The idea of a common mechanism behind different disease processes can extend beyond estrogen related disease processes. While a number of genetic causes of PD have been identified these only account for a small percentage of cases and only very few environmental or modifiable risk factors of PD have been positively confirmed. Examining the entire range of preceding disease diagnoses in PD patients and controls may identify certain previously unsuspected risk factors for PD and provide insight as to common mechanisms behind diseases previously considered unrelated. Therefore, in this study, we will use a matched population based case-control study to compare the risk of PD after preceding diagnoses of the estrogen-related diseases endometriosis and osteoporosis, and also a wide range of disease diagnoses reported by female PD cases in the Danish National Registry of Patients.

### Methods

#### Population and sample

The base population of this study is female Danish citizens identified in the Central Population Registry between 1982 and 2007. All Danish citizens are assigned a unique Central Population Registry (CPR) identification number which can be used to link the national registries. The Danish National Registry of Patients records all hospital admissions after 1977 and all outpatient and emergency visits after 1995. Each visit is identified with the CPR number of the patient, the date of the visit or hospital discharge, and a code for the primary diagnosis. A total of 12,247 female Parkinson’s disease cases were identified by searching the Danish National Registry of Patients for a first instance of a PD diagnostic code (ICD-8: 342, ICD-10: G20) recorded between 1982 and 2007. Ten controls matched to each case by birth year, being alive and PD free at the time of PD diagnosis (index date) of the matched case, were selected using risk-set sampling from the Central Population Registry using their unique CPR number. Cases or controls were excluded when a diagnostic code for one of the following diseases was reported before the index date: Parkinsonism or secondary Parkinsonism (n = 159), unspecified motor neuron disease (n = 9),...
or unspecified hereditary neuromuscular disorder (n = 5) to avoid misclassification. After these exclusions a final sample of 12,093 cases and 122,411 controls remained.

Data collection
The exposure variables relating to preceding disease diagnoses were also derived from the National Registry of Patients. For each case and control, the date and diagnostic code for all recorded hospital discharges or outpatient visits between 1977 and the index date of each subject were collected. This information was then used to create the estrogen related or other disease related exposure variables.

Analytic variables
First, exposure variables were created for two estrogen related diseases, endometriosis and osteoporosis. Subjects were coded as positive for endometriosis if an endometriosis diagnostic code (ICD-10: N80; ICD-8: 625.3) was recorded more than five years before their index date for the study. If no endometriosis diagnostic codes were recorded for a subject, or the codes were first recorded within five years of the index date, then the subject was coded as negative for endometriosis. The induction period of five years was selected to allow for some variation around an average lag of two years observed between the onset of the first symptoms of PD and clinical diagnosis of PD.29 The same method and induction time of between the onset of the first symptoms of PD and clinical diagnosis of PD resulted in a maximum of one case of endometriosis per subject. The same exclusion criteria were repeated stratifying the sample into older (≥75 years) and younger age-at-index date (<75 years) groups. To identify new associations between PD and other preceding and other disease related exposure variables, a second variable was created, which included the above osteoporosis diagnostic codes as well as codes for hip, spine, and forearm fractures which are typically associated with osteoporosis (ICD-10: S120–S129, S220–S221, S320–S328, S520–S529, S720–S721; ICD-8: 805, 808, 813, 820).30,31

The Danish National Registry of Patients includes diagnosis codes based on both ICD-8 (1977–1993) and ICD-10 (1993–present). There are over 10,000 different diagnostic codes used in the registry. To create exposure variables for all other preceding disease diagnoses, these individual ICD codes were grouped into disease categories based on the ICD-8 list of 300 causes for tabulation of hospital morbidity and the ICD-10 tabulation list for morbidity. All ICD codes are assigned to a single morbidity category in each of these tabulation lists, allowing a morbidity category to be identified for each ICD-8 and ICD-10 code from the registry of patients. The morbidity categories of the two tabulation lists were compared, and in many cases, the categories remained the same from ICD-8 to ICD-10 allowing the categories to be directly combined. In other cases, multiple categories from the ICD-8 tabulation list needed to be combined into one category to be consistent with the ICD-10 tabulation list, and vice versa. Diagnostic codes and categories relating to external causes or injuries and routine hospital visits were excluded. A final list of 202 categories combining the ICD-10 and ICD-8 diagnostic codes was identified (see Appendix Table S1) and each case and control was defined as positive or negative for each disease category based on whether they had a recorded diagnostic code for that category more than five years before their index date.

Analytic methods
The distribution of ages and years of enrollment were determined for the cases and controls. The proportion of cases and controls with endometriosis and osteoporosis were calculated, and conditional logistic regression (CLR) was used to calculate the odds ratios (OR) for risk of PD after diagnosis of endometriosis and osteoporosis individually, conditioning on year of birth and year of enrollment. In addition, the CLRs were repeated stratifying the sample into older (>75 years) and younger age-at-index date (≤75 years) groups. To identify new associations between PD and other preceding conditions, CLR was similarly used to calculate the OR for risk of PD associated with each of the 202 morbidity categories, conditioning on year of birth and year of enrollment.

In order to identify the robust associations from the over 200 associations produced by this analysis, Empirical

| Table 1 Distributions of ages and year of enrollment for female Parkinson's disease cases identified from the Danish National Registry of Patients between 1982 and 2007 and matched controls |
|-----------------|-----------------|-----------------|
|                 | Cases n = 12093 | Controls n = 122411 |
| Age range, years |                 |                 |
| <40             | 55 (<1%)        | 546 (<1%)       |
| 41–50           | 145 (1%)        | 1505 (1%)       |
| 51–60           | 557 (5%)        | 5527 (5%)       |
| 61–70           | 1972 (16%)      | 20131 (16%)     |
| 71–80           | 5404 (45%)      | 54594 (45%)     |
| 81–90           | 3709 (31%)      | 37565 (31%)     |
| 90+             | 251 (2%)        | 2543 (2%)       |
| Date of admittance Hospital visits |                 |                 |
| 1982–1987       | 3533 (29%)      | 35349 (29%)     |
| 1988–1994       | 3303 (27%)      | 33050 (27%)     |
| Hospital, emergency and outpatient visits |                 |                 |
| 1995–2001       | 3127 (26%)      | 32023 (26%)     |
| 2002–2007       | 2130 (18%)      | 21989 (18%)     |
Bayes (EB) methods\textsuperscript{32} were used to shrink the effect for each morbidity-PD association towards the null in proportion to the variance of the OR. Fifty-five morbidity categories with fewer than five cases were excluded from the EB analysis to provide a baseline level of stability in the estimates. The 147 remaining estimates were used to calculate adjusted \( p \)-values and ORs for each category.

**Results**

The distribution of ages and year of enrollment of the final sample of 12,093 cases and 122,411 controls is shown in Table 1. The average age of diagnosis for the PD cases or enrollment for the matched controls was 75 years (standard deviation [SD] = 9.2). The average time from the beginning of precedent disease recordings in the Danish National Registry of Patients in 1977 until enrollment in the study was 17 years (SD = 7.3).

Endometriosis shows a marginal association with increased risk of PD in the total sample with an OR of 1.37 (95% confidence interval [CI] 0.99–1.90, Table 2a). Stratifying by age at index date suggests that this marginal increase is driven by a stronger positive association with PD in women age 75 and under, with an OR of 1.49 (95% CI of 1.05–2.11), while in women over the age of 75 there is no increase in risk of PD (OR = 0.90, 95% CI of 0.36–2.24). A test of homogeneity of the odds ratios, however, did not show a significant difference between the two groups (\( p = 0.31 \)).

Diagnosis of osteoporosis appears to have no effect on later risk of PD, either in the entire sample or in either age strata, with ORs very close to the null in all cases (Table 2b). Table 2c shows the same results, however, including osteoporotic fractures as well as osteoporosis diagnoses in the definition of the exposure. This definition shows a much higher prevalence of osteoporosis in the population and shows a slight increased risk of PD in women with osteoporosis with an OR of 1.18 (95% CI of 1.08–1.28). This risk appears to be somewhat greater in women age 75 and under at index date, with an OR of 1.35 (95% CI of 1.14–1.61), but also appears in women over the age of 75 (OR = 1.13, 95% CI of 1.03–1.24).

For each of the 147 morbidity categories an effect estimate (the natural log of the odds ratio, (lnOR) was obtained. Figure 1 shows a histogram of these 147 observed effect estimates and the effect estimates are normally distributed. In any random set of predictors, we might expect to see a normal distribution centered around the null with an equal number of positively associated predictors and negatively associated predictors. In this case, however, the distribution of effect sizes is not centered on the null value of zero. Many more morbidity categories were positively associated than were negatively associated, with a mean effect size across all 147 categories of 0.22, SD of 0.25 and a range from -0.53 to 1.15.

Empirical Bayes adjustment was used to shrink the 147 effect estimates towards the mean estimate to identify the robust associations. After adjustment, 23 categories showed an association to PD with \( p < 0.05 \). The original and adjusted ORs and the adjusted \( p \)-value for these 23 categories are shown in Table 3, grouped together by similar pathways or outcomes. Consistent with the distribution seen in Figure 1,
these 23 robust associations were in a casual direction, not protective. The association with the lowest P-value after adjustment was with neurotic, somatoform, and stress related disorders, which had an adjusted OR of 2.16 and adjusted P-value of 1.5E-07.

The 10 morbidity categories with the most protective adjusted ORs are shown in Table 4. Only three morbidity categories showed any protective effect after adjustment and none had P < 0.05. Original and EB adjusted results for all categories are shown in the Appendix Table S2.

Discussion

Endometriosis did not show the hypothesized protective association with PD, in fact the younger category of women demonstrated a moderately increased risk of PD associated with endometriosis in this study. These results suggest that the observed estrogen related effects in these two diseases likely do not work through similar mechanisms. One point to consider is that endometriosis is primarily diagnosed in young women, and is dependent on high circulating levels of estrogen. PD is primarily seen in older women and may be more affected by cumulative estrogen exposure rather than current estrogen levels, suggesting different estrogen related mechanisms of action. Estrogen naturally occurs in many forms, including 17-β estradiol, estrone, and estriol, which circulate at different levels as women age. In older women, circulating levels of estradiol, the most common estrogen during the reproductive years, decrease and estrone becomes the most common estrogen. Therefore, it is also possible that the estrogen related effects of these two diseases may be specifically related to different forms of the hormone.

Another factor may be the limited control for confounding effects of treatments or other by-products of the initial disease process in this study. Women suffering from endometriosis may be treated with oral contraceptives or in severe cases by hysterectomy, which have both been observed in other studies to be associated with increased risk of PD. Further study, including prescription and treatment information, would be warranted for these findings.

It is also of interest to note that the positive association appears to be only in women enrolled into the study before the age of 75. As endometriosis is most commonly diagnosed at a much younger age than PD, it is very likely that the older age group has increased misclassification due to the left censoring of the exposure data at 1977. It is possible this apparent difference in the ORs is due to a bias of the observed effect toward the null in the older group.

On the other hand, osteoporosis (defined with osteoporotic fractures) showed an increased risk of later PD diagnosis in both older and younger women. This result is consistent with the known protective effects of estrogen on both diseases. Notably, unlike endometriosis, both PD and osteoporosis...
tend to occur later in life and may be more likely to work through similar processes. Osteoporosis defined strictly by the registry diagnoses, not including osteoporotic related fractures, did not show any association to later PD risk. This null result could be due to a number of reasons. Diagnoses of osteoporosis are under-reported in the Danish registry of patients, with incident rates approximately 8% of expected, and often patients whose osteoporosis is first identified by an osteoporotic fracture are listed only under the fracture codes. Therefore, using only osteoporosis diagnostic codes likely results in severe misclassification, particularly among younger women. If this misclassification was non-differential, 

Table 3 After EB adjustment, 23 out of 147 tested morbidity categories showed association to PD in the conditional logistic regression analysis with an adjusted \( p \)-value less than 0.05

| Grouping                      | Morbidity category                                      | # Cases | Original OR | EB-Adjusted OR | EB-Adjusted \( p \)-value |
|-------------------------------|---------------------------------------------------------|---------|-------------|----------------|--------------------------|
| Psychological or Behavioral disorders | Neurotic, stress-related and somatoform disorders      | 278     | 2.35        | 2.16           | 1.5E-07                  |
|                               | Depression                                              | 77      | 2.02        | 1.7            | 0.001                    |
|                               | Alcohol-, drug-abuse-related disease                    | 104     | 1.85        | 1.65           | 0.002                    |
|                               | Other mental and behavioral disorders                   | 99      | 1.72        | 1.56           | 0.006                    |
|                               | Mood [affective] disorders                              | 34      | 2.37        | 2.23           | 0.006                    |
|                               | Other diseases of the nervous system                    | 314     | 1.64        | 1.59           | 0.001                    |
| Neurological disorders        | Mental retardation                                      | 22      | 3.15        | 1.68           | 0.007                    |
|                               | Epilepsy                                                | 95      | 1.67        | 1.52           | 0.009                    |
|                               | Migraine                                                | 75      | 1.52        | 1.41           | 0.038                    |
|                               | Alcohol-, drug-abuse-related disease                    | 104     | 1.85        | 1.65           | 0.002                    |
| Alcohol-related disorders     | Acute pancreatitis and other diseases of the pancreas   | 62      | 1.84        | 1.57           | 0.008                    |
|                               | Other diseases of liver and gallbladder                 | 95      | 1.48        | 1.4            | 0.037                    |
|                               | Gastritis and duodenitis                               | 171     | 1.39        | 1.36           | 0.042                    |
|                               | Rheumatism                                              | 327     | 1.56        | 1.52           | 0.004                    |
|                               | Cystitis                                                | 307     | 1.52        | 1.48           | 0.006                    |
| Inflammatory disorders        | Acute pancreatitis and other diseases of the pancreas   | 62      | 1.84        | 1.57           | 0.008                    |
|                               | Other infectious and parasitic diseases                 | 64      | 1.58        | 1.44           | 0.032                    |
|                               | Gastritis and duodenitis                               | 171     | 1.39        | 1.36           | 0.042                    |
|                               | Iodine deficiency-related thyroid disorders             | 210     | 1.45        | 1.41           | 0.02                     |
| Gastro-intestinal, nutritional disorders | Other endocrine, nutritional and metabolic disorders | 302     | 1.38        | 1.36           | 0.034                    |
|                               | Gastritis and duodenitis                               | 171     | 1.39        | 1.36           | 0.042                    |
|                               | Angina pectoris                                         | 326     | 1.48        | 1.45           | 0.01                     |
|                               | Other diseases of the circulatory system                | 51      | 1.8         | 1.52           | 0.016                    |
| Uncategorized                | Diabetes mellitus                                       | 303     | 1.41        | 1.39           | 0.023                    |
|                               | Respiratory tuberculosis                               | 27      | 2.12        | 1.53           | 0.024                    |
|                               | Other ischemic heart diseases                           | 396     | 1.37        | 1.36           | 0.031                    |
|                               | Disorders of menstruation                               | 802     | 1.32        | 1.32           | 0.045                    |

Notes: The number of exposed cases, original OR, adjusted OR, and adjusted \( p \)-value for each category are shown. Morbidity categories are grouped with related categories, and can appear in more than one grouping.

Abbreviations: PD, Parkinson’s disease; CI, confidence interval; OR, odds ratio; EB, empirical Bayes adjustment.

Table 4 The 10 disease categories with the lowest EB adjusted ORs for PD from the 147 conditional logistic regression analyses are shown with the number of exposed cases, original OR, adjusted OR and adjusted \( p \)-value

| Morbidity category                                             | # Cases | Original OR | EB-Adjusted OR | EB-Adjusted \( p \)-value |
|---------------------------------------------------------------|---------|-------------|----------------|--------------------------|
| Retinal detachments and breaks                                | 23      | 0.59        | 0.93           | 0.70                     |
| Other diseases of arteries, arterioles and capillaries        | 97      | 0.84        | 0.93           | 0.67                     |
| Malignant neoplasm of cervix uteri                           | 25      | 0.65        | 0.95           | 0.79                     |
| Pregnancies with abortive outcome                             | 119     | 0.94        | 1.02           | 0.92                     |
| Paralytic ileus and intestinal obstruction without hernia     | 61      | 0.92        | 1.03           | 0.87                     |
| Bronchitis, emphysema and other chronic obstructive pulmonary diseases | 238     | 1.00        | 1.03           | 0.82                     |
| Delivery without mention of complication                      | 72      | 0.92        | 1.04           | 0.84                     |
| Osteoporosis (not including osteoporotic fracture)            | 108     | 0.99        | 1.05           | 0.78                     |
| Crohn’s disease and ulcerative colitis                        | 36      | 0.88        | 1.05           | 0.79                     |
| Other malignant neoplasms of female genital organs            | 25      | 0.82        | 1.05           | 0.79                     |

Abbreviations: PD, Parkinson’s disease; CI, confidence interval; OR, odds ratio; EB, empirical Bayes adjustment.
as expected given the design, it could result in a substantial bias towards the null, explaining the differing results between the two definitions.

However, an alternative explanation could be due to increased fractures in PD cases due to early PD symptoms of postural instability. Postural instability is a classic symptom of PD and can lead to falls in PD cases; one study found a 38% risk of falling in PD cases. However, postural instability is usually characteristic of later stages of PD, with the time until first fall an average of 9 years after the onset of the earliest symptoms, which are typically tremor or bradykinisia. Therefore, it is unlikely that a large number of PD cases would have a PD-related fall five or more years before first appearance of a PD code. Nevertheless, the observed association is small (OR = 1.18) and possible bias should be considered, especially as it may point to a longer preclinical, symptomatic phase of PD than often considered.

Empirical Bayes adjustment was used to identify novel associations warranting further investigation from analyses of 147 selected morbidity categories identified from the national registry of patients. Using a cutoff of an EB adjusted P-value of 0.05 identified 23 morbidity categories of interest. In comparison, using the same P-value cutoff on the unadjusted results would identify 61 categories for follow-up and using a Bonferroni P-value correction for 147 contrasts (P = 0.00034) would have resulted in the identification of 24 categories of interest (Appendix Table S2). The EB method showed a similar reduction in potential false-positive findings as the conventional method, while likely improving the accuracy of the process by using the observed variance of the data to provide more precise estimates of association.

Many of the strongest associations identified after the EB analysis are psychological or neurological disorders (Table 3). Some of these associations, particularly to certain neurological diseases, may be due to long-term misdiagnoses before identifying the case as PD. The strong associations seen between PD and neurotic disorders, depression, and other mental and behavioral disorders more than 5 years before PD diagnosis may suggest that psychological symptoms; which are known to be associated with both PD and dopamine levels, may be noticed in PD patients long before any traditional clinical signs of the disease manifest. Alternatively, this association could also be consistent with a common mechanism causing a susceptibility to loss of neurotransmitters. Examination of mental disorders before PD have shown consistent associations with increased risk of PD in both case-control and cohort studies. A study examining both depression and anxiety disorders before PD found that the increased risk of PD seen after depression was attenuated when restricting depression diagnosis to more than 5 years in the past. Anxiety disorders however, continued to predict increased PD risk even when restricting to a lag of over 20 years between the diagnoses. This pattern suggests depressive disorders may be more likely to represent early signs of PD, while anxiety disorders may be more likely to be associated with a casual mechanism.

Several of the other most strongly associated preceding conditions could be grouped together with other related conditions. Alcohol abuse, as well as liver disease and pancreatitis (diseases often associated with alcohol abuse), show a strong increased risk of subsequent PD. Cirrhosis of the liver, which is often caused by alcohol abuse, has been associated with symptoms of Parkinsonism, and may be associated with the accumulation of excess levels of manganese which is related to the liver disease. These symptoms are distinct from idiopathic PD, although they may cause misclassification of PD cases that would bias the results for these associations, particularly in the liver disease category.

Alcohol use and abuse has been reported in some studies as protective of PD. Nevertheless, the finding of alcohol abuse related diseases positively associated with PD in this sample of Danish women is consistent with a prospective cohort study conducted in the United Kingdom, which found no overall association between alcoholism and PD, although the study did find an OR of 2.7 (95% CI 1.1–6.8) when only women were studied, albeit in a small number of cases. Taken together, these findings are suggestive that the effect of alcohol on PD risk may be sex-specific. Interestingly, several studies have found an association between alcohol consumption and elevated circulating estrogen levels in premenopausal women and postmenopausal women using hormone replacement therapy (HRT) and not using HRT. Also of interest is the finding that several different inflammatory diseases (eg, rheumatism, cystitis, acute pancreatitis among others) associated with later risk of PD. Inflammation has been a topic of considerable study in the pathogenesis of PD, as inflammatory markers have been observed in the brains of PD patients. While the mechanism is uncertain, and continued investigation is examining whether this inflammation is a cause or a by-product of PD related neurodegeneration, these associations to inflammation related (albeit very clinically diverse) diseases could be suggestive of a common inflammation related mechanism. Finally, we also note several diseases related to the gastrointestinal system and malnutrition associated with increased PD risk, which may be suggestive of a malabsorption related mechanism for PD risk.
The distribution of effects seen across the 147 morbidity categories were substantially skewed towards associations with increased risk (Figure 1). Very few associations showed a protective effect. Nevertheless, the most protective or least causal associations (identified in Table 4) are not unexpected findings. The known protective effect of smoking on PD is a likely reason for the nearly negative association between bronchitis, emphysema, and other chronic obstructive pulmonary diseases and PD. Several of the least causally associated categories are estrogen related, including: delivery without complications; pregnancies that had an abortive outcome; and malignant neoplasm of the cervix uteri and other female genital organs, consistent with the original hypothesis of the study, that conditions associated with estrogen may be associated with decreased risk of PD. The lack of protective associations observed in this study may be due to a form of Berkson’s bias in this sample. Berkson’s selection bias is based on the idea that people with two or more medical conditions are more likely to be hospitalized than people with only one medical condition. Higher rates of disease diagnosis may occur in people who seek out medical attention more frequently.

Strengths and limitations
This study is based on national registry data, and thus includes all female PD cases in Denmark, diagnosed between 1982 and 2007, with well-matched controls. All exposure data are also derived from the registry and are not subject to recall bias. Nevertheless, the results of these studies are limited in the ability to control for confounding, in particular by treatments associated with the preceding disease as well as important risk modifiers of PD and other diseases such as smoking. In addition, the use of hospital morbidity categories may provide less than ideal definitions for exposure categories. In some cases, rarer or less well understood diseases with very different causes and etiologies may be combined into one morbidity category. The study is further complicated by the uncertain latent and induction period for PD, although the insight into potential early preclinical signs of PD may be of equal importance to understanding the disease process as the understanding of causal mechanisms. It is not possible to distinguish whether observed associations arise from a causal effect of the preceding disease or from common causal mechanisms underlying the etiology of both PD and the paired diseases.

Conclusion
In conclusion, the findings of a positive association between osteoporosis and PD and the relatively negative association seen to estrogen related morbidity categories in the EB analysis provides further evidence of estrogen related neuro-protection against PD. The finding of no association between endometriosis and PD, however, does not support this protective relationship. The lack of association between PD and endometriosis may indicate different estrogenic effects on the disease process; for example, a neuro-protective mechanism based on long-term estrogen exposure and less dependent on high levels of estrogen at a given time, which may be more influential in endometriosis. In addition, several novel associations to PD were identified using EB analysis, which may lead to future insight into the disease process.

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## Supplementary materials

### Table S1

| Category                              | ICD-codes          |
|---------------------------------------|--------------------|
| Cholera                               | ICD-10: A00.0–A00.9 |
|                                       | ICD-8: 0.0–0.9      |
| Typhoid and paratyphoid fevers        | ICD-10: A01.0–A01.9 |
|                                       | ICD-8: 1.0–1.9      |
|                                       | ICD-8: 2.0–3.9      |
| Other intestinal infectious diseases   | ICD-10: A02.0–A02.9 |
|                                       | ICD-10: A04.0–A05.9 |
|                                       | ICD-10: A07.0–A08.9 |
|                                       | ICD-8: 5.0–5.9      |
|                                       | ICD-8: 7.0–7.9      |
| Shigellosis/Bacillary dysentery       | ICD-10: A03.0–A03.9 |
|                                       | ICD-8: 4.0–4.9      |
| Amoebiasis                            | ICD-10: A06.0–A06.9 |
|                                       | ICD-8: 6.0–6.9      |
| Diarrhea and gastro-enteritis of presumed infectious origin | ICD-10: A09.0–A09.9 |
|                                       | ICD-8: 8.0–9.9      |
| Respiratory tuberculosis              | ICD-10: A15.0–A16.9 |
|                                       | ICD-8: 10.0–12.3    |
|                                       | ICD-8: 12.0–12.9    |
| Other tuberculosis                    | ICD-10: A17.0–A19.9 |
|                                       | ICD-10: B90.0–B90.9 |
|                                       | ICD-8: 13.0–19.9    |
| Plague                                | ICD-10: A20.0–A20.9 |
|                                       | ICD-8: 20.0–20.9    |
| Other bacterial diseases              | ICD-10: A21.0–A22.9 |
|                                       | ICD-10: A24.0–A28.9 |
|                                       | ICD-10: A31.0–A32.9 |
|                                       | ICD-10: A38.0–A38.9 |
|                                       | ICD-10: A42.0–A49.9 |
|                                       | ICD-10: B96.0–B96.9 |
|                                       | ICD-8: 21.0–22.9    |
|                                       | ICD-8: 24.0–27.9    |
|                                       | ICD-8: 30.0–30.9    |
| Brucellosis                            | ICD-10: A22.0–A22.9 |
|                                       | ICD-8: 23.0–23.9    |
| Leprosy                               | ICD-10: A30.0–A30.9 |
|                                       | ICD-10: B92.0–B92.9 |
|                                       | ICD-8: 30.0–30.9    |
| Tetanus                               | ICD-10: A33.0–A33.9 |
|                                       | ICD-10: A34.0–A35.9 |
|                                       | ICD-8: 37.0–37.9    |
| Diphtheria                             | ICD-10: A36.0–A36.9 |
|                                       | ICD-8: 32.0–32.9    |
| Whooping cough                         | ICD-10: A37.0–A37.9 |
|                                       | ICD-8: 33.0–33.9    |
| Meningococcal infection               | ICD-10: A39.0–A39.9 |
|                                       | ICD-8: 36.0–36.9    |
| Septicemia                             | ICD-10: A40.0–A41.9 |
|                                       | ICD-8: 38.0–38.9    |
| Early syphilis                         | ICD-10: A51.0–A51.9 |
|                                       | ICD-8: 91.0–91.9    |

(Continued)

| Category                              | ICD-codes          |
|---------------------------------------|--------------------|
| Other syphilis                         | ICD-10: A50.0–A50.9 |
|                                       | ICD-10: A52.0–A53.9 |
|                                       | ICD-8: 90.0–90.9    |
|                                       | ICD-8: 92.0–97.9    |
| Gonococcal infection                   | ICD-10: A54.0–A54.9 |
|                                       | ICD-8: 98.0–98.9    |
| Other infectious and parasitic diseases | ICD-10: A55.0–A67.9 |
|                                       | ICD-10: A69.0–A70.9 |
|                                       | ICD-10: A74.0–A74.9 |
|                                       | ICD-10: A77.0–A79.9 |
|                                       | ICD-10: B35.0–B49.9 |
|                                       | ICD-10: B58.0–B64.9 |
|                                       | ICD-10: B85.0–B89.9 |
|                                       | ICD-10: B94.0–B94.9 |
|                                       | ICD-10: B99.0–B99.9 |
|                                       | ICD-8: 130.0–136.9  |
|                                       | ICD-8: 139.0–139.9  |
|                                       | ICD-8: 99.0–117.9   |
| Relapsing fevers                       | ICD-10: A68.0–A68.9 |
|                                       | ICD-8: 88.0–88.9    |
| Other viral diseases                   | ICD-10: A71.0–A71.9 |
|                                       | ICD-10: A81.0–A81.9 |
|                                       | ICD-10: A87.0–A89.9 |
|                                       | ICD-10: B00.0–B04.9 |
|                                       | ICD-10: B07.0–B09.9 |
|                                       | ICD-10: B20.0–B25.9 |
|                                       | ICD-10: B27.0–B34.9 |
|                                       | ICD-10: B87.0–B87.9 |
|                                       | ICD-8: 45.0–46.9    |
|                                       | ICD-8: 50.0–54.9    |
|                                       | ICD-8: 57.0–57.9    |
|                                       | ICD-8: 61.0–61.9    |
|                                       | ICD-8: 66.0–66.9    |
|                                       | ICD-8: 68.0–68.9    |
|                                       | ICD-8: 73.0–79.9    |
| Typhus and other rickettioses         | ICD-10: A75.0–A75.9 |
|                                       | ICD-8: 80.0–83.9    |
| Acute poliomyelitis                    | ICD-10: A80.0–A80.9 |
|                                       | ICD-10: B91.0–B91.9 |
|                                       | ICD-8: 40.0–44.9    |
| Rabies                                | ICD-10: A82.0–A82.9 |
|                                       | ICD-8: 71.0–71.9    |
| Viral encephalitis                     | ICD-10: A83.0–A86.9 |
|                                       | ICD-8: 62.0–65.9    |
| Other arthropod-borne viral fevers     | ICD-10: A90.0–A94.9 |
| and viral hemorrhagic fevers           | ICD-10: A96.0–A99.9 |
|                                       | ICD-8: 67.0–67.9    |
| Yellow fever                           | ICD-10: A95.0–A95.9 |
|                                       | ICD-8: 60.0–60.9    |
| Measles                                | ICD-10: B05.0–B05.9 |
|                                       | ICD-8: 55.0–55.9    |
| Rubella                                | ICD-10: B06.0–B06.9 |
|                                       | ICD-8: 56.0–56.9    |
| Hepatitis                              | ICD-10: B15.0–B15.9 |
|                                       | ICD-10: B16.0–B16.9 |
|                                       | ICD-10: B17.0–B17.9 |
|                                       | ICD-8: 70.0–70.9    |

(Continued)
| Category | ICD-codes |
|----------|-----------|
| Mumps    | ICD-10: B26.0–B26.9 |
|          | ICD-8: 72.0–72.9 |
| Malaria  | ICD-10: B50.0–B54.9 |
|          | ICD-8: B40.0–B44.9 |
| Leishmaniasis | ICD-10: B55.0–B55.9 |
|          | ICD-8: B50.0–B55.9 |
| Trypanosomiasis | ICD-10: B56.0–B57.9 |
|          | ICD-8: B60.0–B67.9 |
| Schistosomiasis | ICD-10: B65.0–B65.9 |
|          | ICD-8: 120.0–120.9 |
| Other helminthiases | ICD-10: B66.0–B66.9 |
|          | ICD-10: B68.0–B75.9 |
|          | ICD-10: B77.0–B83.9 |
|          | ICD-8: 121.0–121.9 |
|          | ICD-8: 123.0–125.9 |
|          | ICD-8: 127.0–129.9 |
| Echinococcosis/Hydatidosis | ICD-10: B67.0–B67.9 |
|          | ICD-8: 122.0–122.9 |
| Hookworm diseases/Ankylostomiasis | ICD-10: B76.0–B76.9 |
|          | ICD-8: 126.0–126.9 |
| Malignant neoplasm of lip, oral cavity and pharynx | ICD-10: C00.0–C14.9 |
|          | ICD-8: 140.0–149.9 |
| Malignant neoplasm of other digestive organs and peritoneum | ICD-10: C15.0–C15.9 |
|          | ICD-10: C17.0–C17.9 |
|          | ICD-10: C22.0–C26.9 |
|          | ICD-8: 150.0–150.9 |
|          | ICD-8: 155.0–159.9 |
| Malignant neoplasm of stomach | ICD-10: C16.0–C16.9 |
|          | ICD-8: 151.0–151.9 |
| Malignant neoplasm of colon | ICD-10: C18.0–C18.9 |
|          | ICD-8: 152.0–153.9 |
| Malignant neoplasm of rectosigmoid junction, rectum, anus and anal canal | ICD-10: C19.0–C21.9 |
|          | ICD-8: 154.0–154.9 |
| Other malignant neoplasms of respiratory and intrathoracic organs | ICD-10: C30.0–C31.9 |
|          | ICD-10: C37.0–C39.9 |
| Malignant neoplasm of other and unspecified respiratory organs | ICD-10: C60.0–C60.9 |
|          | ICD-8: 163.0–163.9 |
| Malignant neoplasm of larynx | ICD-10: C32.0–C32.9 |
|          | ICD-8: 161.0–161.9 |
| Malignant neoplasm of trachea, bronchus and lung | ICD-10: C33.0–C34.9 |
|          | ICD-8: 162.0–162.9 |
| Malignant neoplasm of bone and articular cartilage | ICD-10: C40.0–C41.9 |
|          | ICD-8: 170.0–170.9 |
| Malignant neoplasm of skin | ICD-10: C43.0–C43.9 |
|          | ICD-10: C44.0–C44.9 |
|          | ICD-8: 172.0–173.9 |
| Malignant neoplasm of other specified sites | ICD-10: C45.0–C45.9 |
|          | ICD-10: C69.0–C70.9 |
|          | ICD-10: C72.0–C72.9 |
|          | ICD-8: 171.0–171.9 |
|          | ICD-8: 190.0–190.9 |
|          | ICD-8: 192.0–195.9 |
| Malignant neoplasm of breast | ICD-10: C50.0–C50.9 |
|          | ICD-8: 174.0–174.9 |
| Other malignant neoplasms of female genital organs | ICD-10: C51.0–C52.9 |
|          | ICD-10: C56.0–C58.9 |
|          | ICD-8: 181.0–181.9 |
|          | ICD-8: 183.0–183.1 |
|          | ICD-8: 183.0–184.9 |

**Table S1 (Continued)**

| Category | ICD-codes |
|----------|-----------|
| Malignant neoplasm of cervix uteri | ICD-10: C53.0–C53.9 |
|          | ICD-8: 180.0–180.9 |
| Malignant neoplasm of other and unspecified parts of uterus | ICD-10: C54.0–C55.9 |
|          | ICD-8: 182.0–182.9 |
| Other malignant neoplasms of male genital organs | ICD-10: C60.0–C60.9 |
|          | ICD-10: C62.0–C63.9 |
|          | ICD-8: 186.0–186.9 |
| Malignant neoplasm of prostate | ICD-10: C61.0–C61.9 |
|          | ICD-8: 185.0–185.9 |
| Other malignant neoplasms of urinary tract | ICD-10: C64.0–C66.9 |
|          | ICD-10: C68.0–C68.9 |
| Malignant neoplasm of other genitourinary organs | ICD-10: C67.0–C67.9 |
|          | ICD-8: 180.0–188.9 |
| Malignant neoplasm of bladder | ICD-10: C67.0–C67.9 |
|          | ICD-8: 180.0–188.9 |
| Malignant neoplasm of brain | ICD-10: C71.0–C71.9 |
|          | ICD-8: 191.0–191.9 |
| Malignant neoplasm of other, ill-defined, secondary, unspecified and multiple sites | ICD-10: C73.0–C80.9 |
|          | ICD-8: 197.0–199.9 |
| Hodgkin’s disease | ICD-10: C81.0–C81.9 |
|          | ICD-8: 201.0–201.9 |
| Other malignant neoplasms of lymphoid, hematopoietic and related tissue | ICD-10: C82.0–C85.9 |
|          | ICD-10: C88.0–C90.9 |
|          | ICD-8: 196.0–196.9 |
|          | ICD-8: 200.0–200.9 |
|          | ICD-8: 202.0–203.9 |
|          | ICD-8: 208.0–208.9 |
| Leukemia | ICD-10: C91.0–C95.9 |
|          | ICD-8: 204.0–207.9 |
| Other in situ and benign neoplasms and neoplasms of uncertain and unknown behavior | ICD-10: D00.0–D00.9 |
|          | ICD-10: D07.0–D21.9 |
|          | ICD-10: D24.0–D24.9 |
|          | ICD-10: D26.0–D26.9 |
|          | ICD-10: D28.0–D29.9 |
|          | ICD-10: D31.0–D32.9 |
|          | ICD-10: D34.0–D48.9 |
|          | ICD-8: 210.0–215.9 |
|          | ICD-8: 217.0–217.9 |
|          | ICD-8: 219.0–219.9 |
|          | ICD-8: 221.0–222.9 |
|          | ICD-8: 224.0–224.9 |
|          | ICD-8: 226.0–228.9 |
|          | ICD-8: 230.0–239.9 |
| Carcinoma in situ of cervix uteri | ICD-10: D06.0–D06.9 |
|          | ICD-8: 234.0–234.0 |
| Benign neoplasm of skin | ICD-10: D22.0–D23.9 |
|          | ICD-8: 216.0–216.9 |
| Leiomyoma of uterus | ICD-10: D25.0–D25.9 |
|          | ICD-8: 218.0–218.9 |
| Benign neoplasm of ovary | ICD-10: D27.0–D27.9 |
|          | ICD-8: 220.0–220.9 |
| Benign neoplasm of kidney and other urinary organs | ICD-10: D30.0–D30.9 |
|          | ICD-8: 223.0–223.9 |
| Benign neoplasm of brain and other parts of central nervous system | ICD-10: D33.0–D33.9 |
|          | ICD-8: 225.0–225.9 |
| Iron deficiency anemia | ICD-10: D50.0–D50.9 |
|          | ICD-8: 280.0–280.9 |
| Category                                      | ICD-codes                      |
|----------------------------------------------|--------------------------------|
| Other anemias                                | ICD-10: D51.0–D64.9            |
|                                              | ICD-8: 281.0–285.9             |
| Hemorrhagic conditions and other diseases    | ICD-10: D65.0–D77.9            |
| of blood and blood-forming organs            | ICD-8: 286.0–289.9             |
| Other endocrine, nutritional and metabolic    | ICD-10: D80.0–D89.9            |
| disorders                                     | ICD-10: E15.0–E35.9            |
|                                              | ICD-10: E58.0–E63.9            |
|                                              | ICD-10: E65.0–E65.9            |
|                                              | ICD-10: E66.0–E66.9            |
|                                              | ICD-10: E67.0–E85.9            |
|                                              | ICD-10: E87.0–E90.9            |
|                                              | ICD-8: 251.0–258.9             |
|                                              | ICD-8: 270.0–279.9             |
| Other disorders of thyroid                    | ICD-10: E03.0–E04.9            |
|                                              | ICD-10: E05.0–E05.9            |
|                                              | ICD-8: 240.0–241.9             |
|                                              | ICD-8: 243.0–246.9             |
| Iodine-deficiency-related thyroid disorders   | ICD-10: E00.0–E02.9            |
|                                              | ICD-10: E05.0–E05.9            |
|                                              | ICD-8: 249.0–250.9             |
|                                              | ICD-8: 242.0–242.9             |
| Diabetes mellitus                            | ICD-10: E40.0–E47.9            |
|                                              | ICD-10: E50.0–E50.9            |
|                                              | ICD-10: E51.0–E56.9            |
|                                              | ICD-10: E64.0–E64.9            |
|                                              | ICD-8: 260.0–269.9             |
|                                              | ICD-8: 290.0–290.9             |
| Dementia                                      | ICD-10: F00.0–F03.9            |
|                                              | ICD-10: G31.0–G31.0            |
|                                              | ICD-8: 290.0–290.9             |
| Other mental and behavioral disorders         | ICD-10: F04.0–F09.9            |
|                                              | ICD-10: F50.0–F69.9            |
|                                              | ICD-10: F80.0–F99.9            |
|                                              | ICD-8: 292.0–294.9             |
|                                              | ICD-8: 297.0–299.9             |
|                                              | ICD-8: 305.0–309.9             |
| Alcohol-, drug-abuse-related disease         | ICD-10: F10.0–F19.9            |
|                                              | ICD-8: 291.0–291.9             |
|                                              | ICD-8: 303.0–304.9             |
| Schizophrenia, schizotypal and delusional     | ICD-10: F20.0–F29.9            |
| disorders                                     | ICD-8: 295.0–295.9             |
| Mood [affective] disorders                   | ICD-10: F30.0–F31.9            |
|                                              | ICD-10: F34.0–F39.9            |
|                                              | ICD-8: 296.0–296.1             |
|                                              | ICD-8: 296.0–296.9             |
| Depression                                   | ICD-10: F22.0–F23.9            |
|                                              | ICD-8: 296.0–296.0             |
|                                              | ICD-8: 296.0–296.2             |
| Neurotic, stress-related and somatoform       | ICD-10: F40.0–F48.9            |
| disorders                                     | ICD-8: 300.0–302.9             |
| Mental retardation                           | ICD-10: F70.0–F79.9            |
|                                              | ICD-8: 310.0–315.9             |
| Inflammatory diseases of the central nervous  | ICD-10: G00.0–G09.9            |
| system                                       | ICD-8: 320.0–320.9             |
|                                              | ICD-8: 321.0–324.9             |

(Continued)
### Disease diagnoses preceding Parkinson's disease

| Category                                      | ICD-codes       |
|-----------------------------------------------|-----------------|
| Angina pectoris                               | ICD-10: 120.0–120.9, ICD-8: 413.0–413.9 |
| Acute myocardial infarction                   | ICD-10: 121.0–122.9, ICD-8: 410.0–410.9 |
| Other ischemic heart diseases                 | ICD-10: 123.0–125.9, ICD-8: 411.0–412.9 |
| Other ischemic heart disease                  | ICD-10: 414.0–414.9 |
| Pulmonary embolism                            | ICD-10: 450.0–450.9 |
| Other heart diseases                          | ICD-10: 127.0–143.9, ICD-8: 420.0–426.9 |
| Conduction disorders and cardiac arrhythmias  | ICD-10: 144.0–149.9, ICD-8: 427.0–427.9 |
| Congestive heart failure                      | ICD-10: 150.0–150.9, ICD-8: 427.0–427.0 |
| Intracranial hemorrhage                       | ICD-10: 160.0–162.9, ICD-8: 431.0–431.9 |
| Cerebral infarction                           | ICD-10: 163.0–163.9, ICD-8: 432.0–434.9 |
| Other cerebrovascular diseases                | ICD-10: 164.0–164.9, ICD-8: 430.0–430.9 |
| Intracranial hemorrhage                       | ICD-10: 165.0–165.9, ICD-8: 430.0–430.9 |
| Cerebral infarction                           | ICD-10: 166.0–166.9, ICD-8: 430.0–430.9 |
| Other cerebrovascular diseases                | ICD-10: 167.0–167.9, ICD-8: 430.0–430.9 |
| Heart failure                                 | ICD-10: 151.0–152.9, ICD-8: 420.0–426.9 |
| Atherosclerosis                               | ICD-10: 170.0–170.9, ICD-8: 440.0–440.9 |
| Other diseases of arteries, arterioles and capillaries | ICD-10: 171.0–172.9, ICD-8: 174.0–174.9 |
| Varicose veins of lower extremities           | ICD-10: 183.0–183.9, ICD-8: 454.0–454.9 |
| Hemorrhoids                                   | ICD-10: 184.0–184.9, ICD-8: 455.0–455.9 |
| Other diseases of the circulatory system      | ICD-10: 185.0–189.9, ICD-8: 456.0–458.9 |
| Other acute upper respiratory infections       | ICD-10: 186.0–189.9, ICD-8: 456.0–458.9 |
| Acute pharyngitis and acute tonsillitis       | ICD-10: 187.0–187.9, ICD-8: 456.0–458.9 |
| Influenza                                     | ICD-10: 190.0–190.9, ICD-8: 460.0–461.9 |
| Pneumonia                                     | ICD-10: 191.0–191.9, ICD-8: 460.0–461.9 |
| Acute bronchitis and acute bronchiolitis      | ICD-10: 192.0–192.9, ICD-8: 460.0–461.9 |

### Table S1 (Continued)

| Category                                      | ICD-codes       |
|-----------------------------------------------|-----------------|
| Other diseases of the respiratory system      | ICD-10: J20.0–J22.9, ICD-8: J66.0–J69.9 |
| Other diseases of the upper respiratory tract | ICD-10: J30.0–J31.9, ICD-8: J33.0–J34.9 |
| Bronchitis, emphysema and other chronic obstructive pulmonary diseases | ICD-10: J40.0–J44.9, ICD-8: J45.0–J46.9 |
| Bronchiectasis                                | ICD-10: J47.0–J47.9, ICD-8: 518.0–518.9 |
| Pneumoconioses and related diseases           | ICD-10: J60.0–J65.9, ICD-8: 515.0–516.9 |
| Other diseases of the teeth, oral cavity, salivary glands and jaws | ICD-10: K00.0–K14.9, ICD-8: 520.0–529.9 |
| Other diseases of esophagus, stomach and duodenum | ICD-10: K20.0–K23.9, ICD-8: 528.0–K28.9 |
| Other diseases of the digestive system         | ICD-10: K35.0–K38.9, ICD-8: 535.0–535.9 |
| Gastric and duodenal ulcer                    | ICD-10: K25.0–K27.9, ICD-8: 531.0–534.9 |
| Gastritis and duodenitis                      | ICD-10: K29.0–K29.9, ICD-8: 535.0–535.9 |
| Crohn’s disease and ulcerative colitis        | ICD-10: K50.0–K51.9, ICD-8: 563.0–563.9 |
| Other diseases of the digestive system         | ICD-10: K52.0–K55.9, ICD-8: 570.0–K57.9 |
| Paralytic ileus and intestinal obstruction     | ICD-10: K66.0–K56.9, ICD-8: 560.0–560.9 |
| Other diseases of liver and gallbladder        | ICD-10: K70.0–K77.9, ICD-8: 560.0–560.9 |
| Choledolithiasis and cholecystitis             | ICD-10: K80.0–K81.9, ICD-8: 564.0–569.9 |
| Acute pancreatitis and other diseases of the pancreas | ICD-10: K85.0–K86.9, ICD-8: 570.0–579.9 |
| Infections of the skin and subcutaneous tissue | ICD-10: L00.0–L08.9, ICD-8: 580.0–686.9 |
| Other diseases of the skin and subcutaneous tissue | ICD-10: L10.0–L19.9, ICD-8: 690.0–698.9 |
| |
| Category | ICD-codes |
|----------|-----------|
| Other disorders of joints | ICD-10: M00.0–M03.9  
ICD-10: M22.0–M25.9  
ICD-8: 724.0–724.9  
ICD-8: 726.0–727.9  
ICD-8: 729.0–729.9  
ICD-8: 737.0–737.9 |
| Rheumatoid arthritis and other inflammatory polyarthropathies | ICD-10: M05.0–M14.9  
ICD-8: 712.0–712.9  
ICD-8: 714.0–714.9  
ICD-8: 716.0–716.9  
ICD-8: 718.0–718.9  
ICD-8: 721.0–721.9  
ICD-8: 723.0–723.9 |
| Osteoarthritis and allied conditions | ICD-10: M15.0–M19.9  
ICD-8: 710.0–711.9  
ICD-8: 713.0–715.9  
ICD-8: 716.0–716.9  
ICD-8: 718.0–718.9  
ICD-8: 720.0–720.9  
ICD-8: 722.0–722.9  
ICD-8: 724.0–724.9  
ICD-8: 726.0–726.9  |
| Acquired deformities of limbs | ICD-10: M20.0–M21.9  
ICD-8: 736.0–736.9 |
| Other diseases of the musculoskeletal system and connective tissue | ICD-10: M22.0–M25.9  
ICD-8: 724.0–724.9  
ICD-8: 726.0–727.9  
ICD-8: 729.0–729.9  
ICD-8: 737.0–737.9  |
| Other dorsopathies | ICD-10: M40.0–M41.9  
ICD-10: M43.0–M43.5  
ICD-10: M43.7–M43.9  
ICD-10: M44.0–M44.9  
ICD-10: M48.3–M48.3  
ICD-8: 735.0–735.9  
ICD-8: 738.0–738.9  |
| Osteochondrosis | ICD-10: M42.0–M42.9  
ICD-10: M91.0–M93.9  
ICD-8: 722.0–722.9  |
| Rheumatism | ICD-10: M43.0–M43.5  
ICD-10: M46.0–M46.9  
ICD-10: M48.3–M48.3  
ICD-8: 735.0–735.9  
ICD-8: 738.0–738.9  |
| Cervical and other intervertebral disk disorders | ICD-10: M50.0–M51.9  
ICD-10: M54.0–M54.9  
ICD-8: 725.0–725.9  
ICD-8: 728.0–728.9  |
| Myositis | ICD-10: M60.0–M60.9  
ICD-8: 722.0–722.9  
ICD-8: 724.0–725.9  
ICD-8: 728.0–728.9  |
| Soft tissue disorders | ICD-10: M61.0–M69.9  
ICD-10: M79.0–M79.9  
ICD-8: 717.0–718.9  
ICD-8: 719.0–719.9  
ICD-8: 720.0–720.9  
ICD-8: 722.0–722.9  
ICD-8: 724.0–724.9  
ICD-8: 726.0–726.9  |
| Osteoporosis with and without fracture | ICD-10: M80.0–M81.9  
ICD-8: 723.0–723.0  
ICD-8: 721.0–721.9  
ICD-8: 723.0–723.9  |
| Other diseases of bone | ICD-10: M82.0–M85.9  
ICD-10: M89.0–M89.9  
ICD-8: 720.0–720.9  
ICD-8: 722.0–722.9  |
| Osteomyelitis and periostitis | ICD-10: M86.0–M86.9  
ICD-8: 720.0–720.9  
ICD-8: 722.0–722.9  |
| Nephritis and nephrosis | ICD-10: N00.0–N08.9  
ICD-8: 580.0–584.9 |
| Infections of kidney | ICD-10: N10.0–N16.9  
ICD-8: 590.0–590.9  
ICD-8: 591.0–591.9 |
| Other diseases of the urinary system | ICD-10: N17.0–N19.9  
ICD-10: N25.0–N29.9  
ICD-10: N31.0–N39.9  
ICD-8: 651.0–651.9  
ICD-8: 670.0–670.9 |
| (Continued) | (Continued) |
**Table S1 (Continued)**

| Category                                              | ICD-codes               |
|-------------------------------------------------------|-------------------------|
| Delivery without mention of complication              | ICD-10: O80.0–O80.9     |
|                                                       | ICD-8: 650.0–650.9      |
| Conditions originating in the perinatal period        | ICD-10: P00.0–P54.9     |
|                                                       | ICD-10: P56.0–P96.9     |
|                                                       | ICD-8: 760.0–773.9      |
|                                                       | ICD-8: 776.0–779.9      |
| Hemolytic disease of fetus and newborn                | ICD-10: P55.0–P55.9     |
|                                                       | ICD-8: 774.0–775.9      |
|                                                       | ICD-8: 741.0–742.9      |
| Spina bifida and congenital hydrocephalus             | ICD-10: Q05.0–Q05.9     |
|                                                       | ICD-8: 741.0–742.9      |
| Congenital malformations of the circulatory system    | ICD-10: Q20.0–Q28.9     |
|                                                       | ICD-8: 746.0–747.9      |
| Cleft lip and cleft palate                            | ICD-10: Q35.0–Q37.9     |
|                                                       | ICD-8: 749.0–749.9      |
| Other congenital malformations of the digestive system| ICD-10: Q38.0–Q40.9     |
|                                                       | ICD-10: Q42.0–Q45.9     |
|                                                       | ICD-8: 750.0–750.0      |
|                                                       | ICD-8: 750.0–750.9      |
|                                                       | ICD-8: 751.0–751.9      |
| Absence, atresia and stenosis of small intestine      | ICD-10: Q41.0–Q41.9     |
|                                                       | ICD-8: 750.0–750.1      |
| Other malformations of the genitourinary system       | ICD-10: Q50.0–Q52.9     |
|                                                       | ICD-10: Q54.0–Q64.9     |
|                                                       | ICD-8: 752.2–753.9      |

(Continued)
Table S2 All 147 morbidity categories with 5 or more cases of PD are shown with the number of exposed cases, original OR and P-value, and EB adjusted odds ratio and P-value.

| Category                                                      | # Cases | Original OR | Original P-value | Adjusted OR | Adjusted P-value |
|---------------------------------------------------------------|---------|-------------|------------------|-------------|------------------|
| Neurotic, stress-related and somatoform disorders              | 278     | 2.35        | <0.0001          | 2.16        | 1.5 x 10^-7      |
| Other diseases of the nervous system                           | 314     | 1.64        | <0.0001          | 1.59        | 0.001            |
| Depression                                                    | 77      | 2.02        | <0.0001          | 1.7         | 0.001            |
| Alcohol-, drug-abuse-related disease                          | 104     | 1.85        | <0.0001          | 1.65        | 0.002            |
| Rheumatism                                                    | 327     | 1.56        | <0.0001          | 1.52        | 0.004            |
| Other mental and behavioral disorders                         | 99      | 1.72        | <0.0001          | 1.56        | 0.006            |
| Mood [affective] disorders                                    | 34      | 2.37        | <0.0001          | 1.65        | 0.006            |
| Cystitis                                                      | 307     | 1.52        | <0.0001          | 1.48        | 0.006            |
| Mental retardation                                            | 22      | 3.15        | <0.0001          | 1.68        | 0.007            |
| Acute pancreatitis and other diseases of the pancreas         | 62      | 1.84        | <0.0001          | 1.57        | 0.008            |
| Epilepsy                                                      | 95      | 1.67        | <0.0001          | 1.52        | 0.009            |
| Angina pectoris                                               | 326     | 1.48        | <0.0001          | 1.45        | 0.01             |
| Other diseases of the circulatory system                      | 51      | 1.8         | 0.0001           | 1.52        | 0.016            |
| Iodine-deficiency-related thyroid disorders                    | 210     | 1.45        | <0.0001          | 1.41        | 0.02             |
| Diabetes mellitus                                             | 303     | 1.41        | <0.0001          | 1.39        | 0.023            |
| Respiratory tuberculosis                                      | 27      | 2.12        | 0.0004           | 1.53        | 0.024            |
| Other ischemic heart diseases                                 | 396     | 1.37        | <0.0001          | 1.36        | 0.031            |
| Other infectious and parasitic diseases                       | 64      | 1.58        | 0.0007           | 1.44        | 0.032            |
| Other endocrine, nutritional and metabolic disorders          | 302     | 1.38        | <0.0001          | 1.36        | 0.034            |
| Other diseases of liver and gallbladder                       | 95      | 1.48        | 0.0004           | 1.4         | 0.037            |
| Migraine                                                     | 75      | 1.52        | 0.0009           | 1.41        | 0.038            |
| Gastritis and duodenitis                                      | 171     | 1.39        | <0.0001          | 1.36        | 0.042            |
| Disorders of menstruation                                     | 802     | 1.32        | <0.0001          | 1.32        | 0.045            |
| Other diseases of esophagus stomach and duodenum              | 177     | 1.36        | 0.0001           | 1.34        | 0.053            |
| Congenital malformations of the circulatory system            | 16      | 2.27        | 0.003            | 1.46        | 0.053            |
| Nephritis and nephrosis                                       | 19      | 2.06        | 0.0042           | 1.45        | 0.054            |
| Inflammatory diseases of the central nervous system            | 22      | 1.93        | 0.0048           | 1.44        | 0.054            |
| Congestive heart failure                                      | 155     | 1.36        | 0.0004           | 1.33        | 0.06             |
| Infections of the skin and subcutaneous tissue                | 109     | 1.39        | 0.0014           | 1.35        | 0.061            |
| Dementia                                                      | 53      | 1.5         | 0.006            | 1.38        | 0.062            |
| Strabismus                                                    | 33      | 1.59        | 0.0134           | 1.39        | 0.074            |
| Other diseases of the digestive system                        | 556     | 1.29        | <0.0001          | 1.28        | 0.074            |
| Diarrhea and gastro-enteritis of presumed infectious origin   | 106     | 1.35        | 0.0036           | 1.32        | 0.08             |
| Influenza                                                     | 45      | 1.47        | 0.0167           | 1.35        | 0.086            |
| Avitaminosis and other nutritional deficiency                 | 22      | 1.7         | 0.0217           | 1.38        | 0.088            |
| Acute pharyngitis and acute tonsillitis                       | 21      | 1.72        | 0.0221           | 1.38        | 0.089            |
| Other tuberculosis                                            | 20      | 1.73        | 0.0237           | 1.38        | 0.092            |
| Other disorders of genitourinary tract                        | 229     | 1.28        | 0.0005           | 1.28        | 0.098            |
| Other disorders of thyroid                                    | 259     | 1.28        | 0.0002           | 1.27        | 0.099            |
| Other anemias                                                 | 100     | 1.32        | 0.0086           | 1.3         | 0.102            |
| Malignant neoplasm of other and unspecified parts of uterus   | 108     | 1.32        | 0.0073           | 1.3         | 0.103            |
| Abdominal and pelvic pain                                     | 213     | 1.27        | 0.0011           | 1.27        | 0.113            |
| Essential (primary) hypertension                              | 458     | 1.25        | <0.0001          | 1.25        | 0.113            |
| Other diseases of the urinary system                          | 189     | 1.27        | 0.0019           | 1.27        | 0.115            |
| Iron deficiency anemia                                       | 65      | 1.33        | 0.03             | 1.3         | 0.124            |
| Benign neoplasm of brain and other parts of central nervous system | 31  | 1.43        | 0.062            | 1.32        | 0.132            |
| Conditions originating in the perinatal period                | 7       | 2.55        | 0.0303           | 1.36        | 0.133            |
| Endometriosis                                                 | 42      | 1.37        | 0.0551           | 1.3         | 0.134            |
| Transient cerebral ischemic attacks and related syndromes     | 144     | 1.26        | 0.01             | 1.25        | 0.142            |
| Gastric and duodenal ulcer                                    | 278     | 1.23        | 0.0012           | 1.23        | 0.151            |
| Malignant neoplasm of other, ill-defined, secondary, unspecified, multiple sites | 25 | 1.42        | 0.0999           | 1.31        | 0.155            |
| Malignant neoplasm of bladder                                 | 22      | 1.44        | 0.1074           | 1.31        | 0.158            |
Disease diagnoses preceding Parkinson’s disease

Table S2 (Continued)

| Category                                                                 | # Cases | Original OR | Original P-value | Adjusted OR | Adjusted P-value |
|-------------------------------------------------------------------------|---------|-------------|------------------|-------------|------------------|
| Hemorrhagic conditions and other diseases of blood and blood-forming organs | 34      | 1.35        | 0.1043           | 1.29        | 0.166            |
| Hemorrhoids                                                             | 155     | 1.23        | 0.0168           | 1.23        | 0.176            |
| Septicemia                                                              | 31      | 1.34        | 0.125            | 1.28        | 0.176            |
| Other congenital malformations of the digestive system                  | 12      | 1.58        | 0.1397           | 1.31        | 0.177            |
| Other inflammatory diseases of female pelvic organs                     | 87      | 1.25        | 0.0519           | 1.24        | 0.178            |
| Other viral diseases                                                    | 89      | 1.24        | 0.0565           | 1.24        | 0.186            |
| Other peripheral vascular diseases                                       | 26      | 1.35        | 0.1562           | 1.28        | 0.188            |
| Other diseases of bone                                                  | 26      | 1.34        | 0.1574           | 1.28        | 0.188            |
| Soft tissue disorders                                                   | 219     | 1.21        | 0.0096           | 1.21        | 0.192            |
| Hernia                                                                 | 296     | 1.2        | 0.0032           | 1.21        | 0.194            |
| Pulmonary embolism                                                      | 50      | 1.26        | 0.1288           | 1.25        | 0.202            |
| Leukemia                                                                | 10      | 1.52        | 0.2144           | 1.29        | 0.207            |
| Other diseases of the eye and adnexa                                     | 264     | 1.19        | 0.0083           | 1.2        | 0.216            |
| Malignant neoplasm of stomach                                           | 11      | 1.45        | 0.2499           | 1.28        | 0.217            |
| Acute rheumatic fever                                                    | 8       | 1.56        | 0.2437           | 1.29        | 0.218            |
| Cervical and other intervertebral disk disorders                        | 377     | 1.18        | 0.0027           | 1.19        | 0.227            |
| Acute bronchitis and acute bronchiolitis                                | 51      | 1.23        | 0.1642           | 1.23        | 0.227            |
| Acute poliomyelitis                                                     | 8       | 1.5        | 0.2839           | 1.28        | 0.229            |
| Female genital prolapse                                                 | 582     | 1.18        | 0.0003           | 1.18        | 0.232            |
| Other malignant neoplasms of lymphoid, hematopoietic and related tissue | 38      | 1.23        | 0.2248           | 1.23        | 0.239            |
| Osteomyelitis and periostitis                                           | 14      | 1.32        | 0.3293           | 1.26        | 0.244            |
| Malignant neoplasm of colon                                             | 73      | 1.2        | 0.1426           | 1.21        | 0.245            |
| Schizophrenia, schizotypal and delusional disorders                     | 9       | 1.4        | 0.348            | 1.26        | 0.246            |
| Malignant neoplasm of other specified sites                             | 17      | 1.28        | 0.3412           | 1.25        | 0.251            |
| Other dorsopathies                                                      | 63      | 1.2        | 0.1802           | 1.21        | 0.255            |
| Chronic disease of tonsils and adenoids                                 | 14      | 1.29        | 0.3818           | 1.25        | 0.259            |
| Conduction disorders and cardiac arrhythmias                            | 326     | 1.17        | 0.0092           | 1.18        | 0.26             |
| Other intestinal infectious diseases                                     | 8       | 1.33        | 0.4449           | 1.25        | 0.269            |
| Other diseases of the ear and mastoid process                           | 379     | 1.16        | 0.0085           | 1.17        | 0.271            |
| Phlebitis, thrombophlebitis, venous embolism and thrombosis             | 133     | 1.17        | 0.0871           | 1.19        | 0.272            |
| Other diseases of the musculoskeletal system and connective tissue      | 154     | 1.17        | 0.0752           | 1.18        | 0.28             |
| Cataract and other disorders of lens                                     | 451     | 1.15        | 0.006            | 1.16        | 0.289            |
| Pneumonia                                                               | 264     | 1.16        | 0.029            | 1.17        | 0.293            |
| Other bacterial diseases                                                | 56      | 1.17        | 0.274            | 1.2        | 0.297            |
| Other inflammatory diseases of eye                                      | 62      | 1.16        | 0.2832           | 1.19        | 0.313            |
| Other malformations of the genitourinary system                         | 24      | 1.16        | 0.4998           | 1.21        | 0.32             |
| Inflammatory disease of cervix uteri                                    | 21      | 1.16        | 0.5317           | 1.21        | 0.322            |
| Benign neoplasm of kidney and other urinary organs                      | 32      | 1.14        | 0.4716           | 1.19        | 0.331            |
| Malignant neoplasm of other genitourinary organs                        | 12      | 1.14        | 0.6703           | 1.21        | 0.332            |
| Ectopic pregnancy                                                       | 11      | 1.14        | 0.6928           | 1.21        | 0.332            |
| Leiomyoma of uterus                                                     | 226     | 1.14        | 0.0711           | 1.15        | 0.333            |
| Female infertility                                                      | 13      | 1.11        | 0.7316           | 1.2        | 0.35             |
| Hepatitis                                                               | 5       | 1           | 0.9949           | 1.21        | 0.364            |
| Malignant neoplasm of skin                                              | 68      | 1.12        | 0.3765           | 1.16        | 0.371            |
| Disorders of breast                                                     | 170     | 1.12        | 0.1573           | 1.14        | 0.375            |
| Bronchiectasis                                                          | 5       | 0.95        | 0.9209           | 1.2        | 0.379            |
| Other diseases of ovary, fallopian tube and parametrium                 | 79      | 1.11        | 0.3682           | 1.15        | 0.386            |
| Urolithiasis/Calcus of urinary system                                   | 101     | 1.12        | 0.2983           | 1.15        | 0.387            |
| Malignant neoplasm of trachea, bronchus and lung                        | 13      | 1.04        | 0.8886           | 1.18        | 0.393            |
| Typhoid and paratyphoid fevers                                         | 5       | 0.86        | 0.7477           | 1.19        | 0.412            |
| Benign neoplasm of ovary                                                | 108     | 1.11        | 0.3277           | 1.14        | 0.413            |
| Other in situ and benign neoplasms or of uncertain/unknown behavior     | 596     | 1.11        | 0.0191           | 1.12        | 0.42             |
| Other diseases of upper respiratory tract                                | 95      | 1.1         | 0.3793           | 1.14        | 0.42             |

(Continued)
Table S2 (Continued)

| Category                                                                 | # Cases | Original OR | Original P-value | Adjusted OR | Adjusted P-value |
|---------------------------------------------------------------------------|---------|-------------|------------------|-------------|------------------|
| Other congenital malformations/deformations of the musculoskeletal system | 22      | 1.05        | 0.8351           | 1.16        | 0.422            |
| Glaucoma                                                                  | 111     | 1.09        | 0.3709           | 1.13        | 0.44             |
| Intracranial hemorrhage                                                  | 19      | 1           | 0.9909           | 1.15        | 0.457            |
| Other cerebrovascular diseases                                           | 219     | 1.09        | 0.2137           | 1.11        | 0.464            |
| Diseases of appendix                                                     | 119     | 1.08        | 0.416            | 1.12        | 0.475            |
| Chronic sinusitis                                                        | 18      | 0.97        | 0.8932           | 1.14        | 0.488            |
| Acute myocardial infarction                                              | 235     | 1.09        | 0.2379           | 1.11        | 0.493            |
| Multiple sclerosis and other demyelinating disease                       | 13      | 0.91        | 0.737            | 1.14        | 0.5              |
| Other diseases of the skin and subcutaneous tissue                       | 183     | 1.08        | 0.3258           | 1.11        | 0.501            |
| Carcinoma in situ of cervix uteri                                      | 53      | 1.05        | 0.7547           | 1.12        | 0.501            |
| Cerebral infarction                                                      | 102     | 1.07        | 0.5218           | 1.11        | 0.502            |
| Malignant neoplasm of lip, oral cavity and pharynx                      | 7       | 0.77        | 0.4979           | 1.15        | 0.503            |
| Other complications of pregnancy or delivery                             | 133     | 1.06        | 0.6019           | 1.11        | 0.506            |
| Osteochondrosis                                                          | 21      | 0.95        | 0.8228           | 1.13        | 0.533            |
| Other diseases of the teeth, oral cavity, salivary glands and jaws       | 76      | 1.04        | 0.7218           | 1.11        | 0.544            |
| Malignant neoplasm of breast                                             | 211     | 1.07        | 0.3679           | 1.09        | 0.548            |
| Salpingitis and oophoritis                                               | 20      | 0.93        | 0.7426           | 1.12        | 0.554            |
| Other heart diseases                                                     | 77      | 1.04        | 0.7586           | 1.1         | 0.562            |
| Acquired deformities of limbs                                            | 31      | 0.97        | 0.8887           | 1.11        | 0.564            |
| Osteoarthritis and allied conditions                                     | 692     | 1.07        | 0.0898           | 1.08        | 0.568            |
| Cholelithiasis and cholecystitis                                         | 383     | 1.07        | 0.232            | 1.08        | 0.576            |
| Other and unspecified congenital anomalies                               | 26      | 0.95        | 0.7927           | 1.11        | 0.576            |
| Chronic rheumatic heart disease                                          | 24      | 0.94        | 0.7585           | 1.11        | 0.577            |
| Other diseases of the respiratory system                                  | 90      | 1.03        | 0.7592           | 1.09        | 0.588            |
| Varicose veins of lower extremities                                      | 347     | 1.06        | 0.3149           | 1.08        | 0.605            |
| Other acute upper respiratory infections                                  | 23      | 0.91        | 0.6469           | 1.1         | 0.617            |
| Infections of kidney                                                     | 76      | 1.02        | 0.8962           | 1.09        | 0.62             |
| Other diseases of arteries, arterioles and capillaries                   | 97      | 0.84        | 0.0963           | 0.93        | 0.673            |
| Benign neoplasm of skin                                                  | 31      | 0.91        | 0.6085           | 1.08        | 0.688            |
| Retinal detachments and breaks                                           | 23      | 0.59        | 0.014            | 0.93        | 0.699            |
| Rheumatoid arthritis and other inflammatory polyarthropathies            | 119     | 1.01        | 0.9178           | 1.06        | 0.704            |
| Malignant neoplasm of rectosigmoid junction, rectum, anus, anal canal    | 29      | 0.89        | 0.5322           | 1.07        | 0.713            |
| Atherosclerosis                                                          | 89      | 0.99        | 0.9518           | 1.06        | 0.714            |
| Other disorders of joints                                                | 128     | 1           | 0.9646           | 1.05        | 0.736            |
| Osteoporosis with and without fracture                                    | 108     | 0.99        | 0.8846           | 1.05        | 0.776            |
| Malignant neoplasm of cervix uteri                                      | 25      | 0.65        | 0.0346           | 0.95        | 0.79             |
| Other malignant neoplasms of female genital organs                       | 25      | 0.82        | 0.35             | 1.05        | 0.79             |
| Crohn’s disease and ulcerative colitis                                    | 36      | 0.88        | 0.4703           | 1.05        | 0.792            |
| Bronchitis, emphysema and other chronic obstructive pulmonary diseases   | 238     | 1           | 0.9632           | 1.03        | 0.824            |
| Delivery without mention of complication                                 | 72      | 0.92        | 0.5339           | 1.04        | 0.839            |
| Paralytic ileus and intestinal obstruction without hernia                | 61      | 0.92        | 0.5124           | 1.03        | 0.871            |
| Pregnancies with abortive outcome                                        | 119     | 0.94        | 0.5711           | 1.02        | 0.922            |

Abbreviations: OR, odds ratio; PD, Parkinson’s disease; EB, empirical Bayes.