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ORIGINAL RESEARCH

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

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of women with PD.[2–4] Furthermore, studies have shown some, although not all, factors associated with estrogen, such as hormone replacement therapy,[5] length of fertile life,[6] or receipt of hysterectomy[7] are associated with PD risk. However, other studies have shown no, or an inverse association, to the same or similar factors.[6–10]

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.[11,12] 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;[13,14] however, many studies have reported overall reduced cancer rates or mortality in PD patients.[15–20] 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 endometriosis,[11] as a precedent condition to PD.

Diseases related to decreased estrogen exposure

Osteoporosis is also associated with estrogen; reduced cumulative exposure to estrogen increases the risk of osteoporosis.[21] Osteoporosis has been studied in patients with PD, partially because of the increased likelihood of falls in PD patients that lead to fractures.[22] 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.[22,23] 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,[24,25] as compared with an association to decreased risk of PD.[26] 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.[27] 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.[28]

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 five years was used to create two osteoporosis exposure variables. The first variable was defined strictly from diagnoses of osteoporosis appearing in the registry (Osteoporosis diagnostic codes: ICD-10: M80–M81; ICD-8:723). As osteoporosis may be significantly under-recorded in the registry of patients, 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

All		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[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 = 0.9, 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,

Table 2 Numbers of female Parkinson's disease cases and matched controls with exposure to the estrogen-related diseases, along with ORs and 95% confidence intervals from conditional logistic regression, conditioning on age and birth year **A.** Endometriosis **B.** Osteoporosis by diagnosis **C.** Osteoporosis by diagnosis or osteoporotic fracture

	Total sample		**Age ≤ 75**		**Age > 75**	
A	Endometriosis	No endometriosis	Endometriosis	No endometriosis	Endometriosis	No endometriosis
Cases	42	12051	37	5056	5	6995
Controls	315	122096	258	51438	57	70658
OR (95% CI)	1.37 (0.99–1.90)		1.49 (1.05–2.11)		0.90 (0.36–2.24)	
B	Osteoporosis	No osteoporosis	Osteoporosis	No osteoporosis	Osteoporosis	No osteoporosis
Cases	108	11985	16	5077	92	6908
Controls	1117	121294	185	51511	932	69783
OR (95% CI)	0.99 (0.81–1.20)		0.89 (0.53–1.49)		1.00 (0.81–1.25)	
C	Osteoporosis including osteoporotic fracture	No osteoporosis including osteoporotic fracture	Osteoporosis including osteoporotic fracture	No osteoporosis including osteoporotic fracture	Osteoporosis including osteoporotic fracture	No osteoporosis including osteoporotic fracture
Cases	683	11410	149	4944	534	6466
Controls	6005	116406	1151	50545	4854	65861
OR (95% CI)	1.18 (1.08–1.28)		1.35 (1.14–1.61)		1.13 (1.03–1.24)	

Abbreviations: CI, confidence interval; OR, odds ratio.

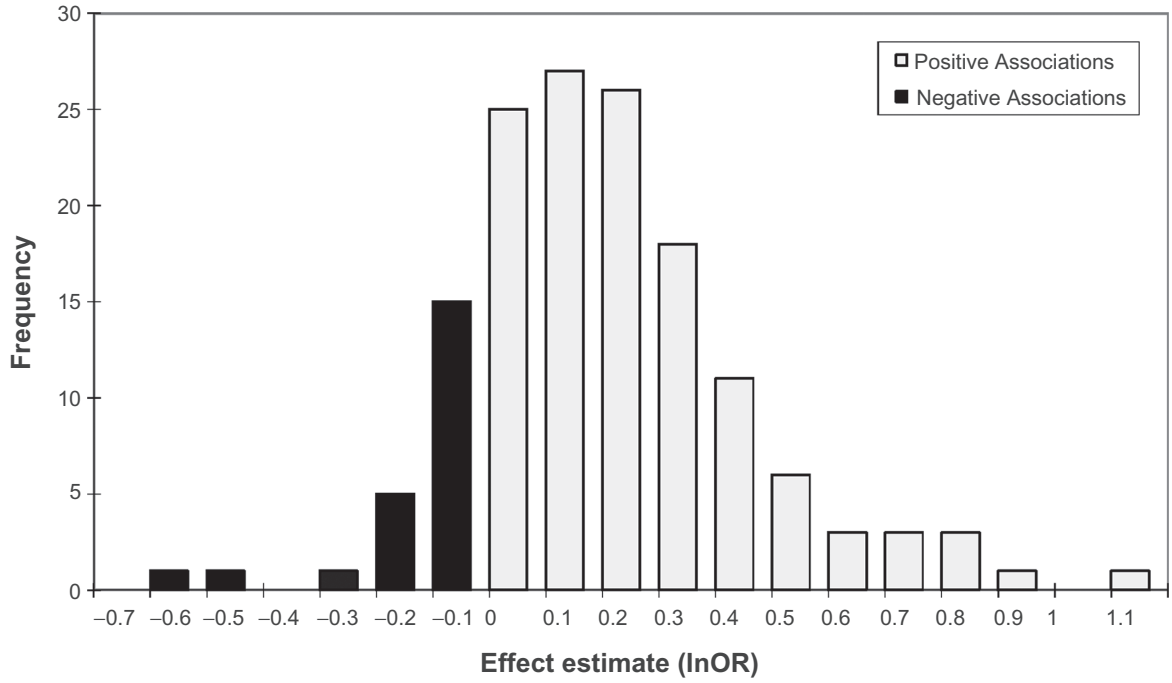

Figure 1 The distribution of effect estimates produced by conditional logistic regression for female Parkinson's disease cases and matched controls on each of 147 morbidity categories derived from the Danish National Registry of Patients diagnostics codes is shown. Effect estimates representing a positive association are shown in grey, while negative associations are shown in black.
Abbreviation: lnOR, the natural log of the odds ratio.

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.[33] PD is primarily seen in older women and may be more affected by cumulative estrogen exposure rather than current estrogen levels,[6,7] 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.[34–36] 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.[7,37] 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

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	1.65	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.

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.[31] Therefore, using only osteoporosis diagnostic codes likely results in severe misclassification, particularly among younger women. If this misclassification was non-differential,

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.[38] 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.[39,40] 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.[41] 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.[42] 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), all 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.[43] 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.[44–46] 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.[47] 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.[48–51]

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.[52] 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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Disclosures

The authors reports no conflicts of interest relevant to this work.

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Supplementary materials

Table S1 List of 202 morbidity categories and associated ICD-8 and ICD-10 codes

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: 31.0–31.9
	ICD-8: 34.0–34.1
	ICD-8: 35.0–35.9
	ICD-8: 39.0–39.9
Brucellosis	ICD-10: A23.0–A23.9
	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
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: 89.0–89.9
	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: B97.0–B97.9
	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 rickettsioses	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 and viral hemorrhagic fevers	ICD-10: A90.0–A94.9
	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–B19.9
	ICD-8: 70.0–70.9

(*Continued*)

Table S1 (*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: 84.0–84.9
Leishmaniasis	ICD-10: B55.0–B55.9
	ICD-8: 85.0–85.9
Trypanosomiasis	ICD-10: B56.0–B57.9
	ICD-8: 86.0–87.9
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-8: 160.0–160.9
	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–C49.9
	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
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-8: 187.0–187.9
	ICD-8: 189.0–189.9
Malignant neoplasm of bladder	ICD-10: C67.0–C67.9
	ICD-8: 188.0–188.9
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-10: C97.0–C97.9
	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-10: C96.0–C96.9
	ICD-8: 196.0–196.9
	ICD-8: 200.0–200.9
	ICD-8: 202.0–203.9
	ICD-8: 208.0–209.9
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–D05.9
	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

(*Continued*)

Table S1 (*Continued*)

Category	ICD-codes
Other anemias	ICD-10: D51.0–D64.9
	ICD-8: 281.0–285.9
Hemorrhagic conditions and other diseases of blood and blood-forming organs	ICD-10: D65.0–D77.9
	ICD-8: 286.0–289.9
Other endocrine, nutritional and metabolic disorders	ICD-10: D80.0–D89.9
	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: E06.0–E07.9
	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: 242.0–242.9
Diabetes mellitus	ICD-10: E10.0–E14.9
	ICD-8: 249.0–250.9
Avitaminosis and other nutritional deficiency	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
Dementia	ICD-10: F00.0–F03.9
	ICD-10: G31.0–G31.0
	ICD-8: 290.0–290.0
	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 disorders	ICD-10: F20.0–F29.9
	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: F32.0–F33.9
	ICD-8: 296.0–296.0
	ICD-8: 296.0–296.2
Neurotic, stress-related and somatoform disorders	ICD-10: F40.0–F48.9
	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 system	ICD-10: G00.0–G09.9
	ICD-8: 320.0–320.9
	ICD-8: 321.0–324.9
Other diseases of the nervous system	ICD-10: G10.0–G13.9
	ICD-10: G21.0–G26.9
	ICD-10: G31.1–G32.9
	ICD-10: G36.0–G37.9
	ICD-10: G44.0–G44.9
	ICD-10: G46.0–G47.9
	ICD-10: G50.0–G73.9
	ICD-10: G80.0–G83.9
	ICD-10: G90.0–G99.9
	ICD-8: 330.0–333.9
	ICD-8: 343.0–344.9
	ICD-8: 347.0–358.9
Parkinson's disease	ICD-10: G20.0–G20.9
	ICD-8: 342.0–342.9
Alzheimer's disease	ICD-10: G30.0–G30.9
	ICD-8: 290.0–290.1
Multiple sclerosis and other demyelinating disease	ICD-10: G35.0–G35.9
	ICD-8: 340.0–341.9
Epilepsy	ICD-10: G40.0–G41.9
	ICD-8: 345.0–345.9
Migraine	ICD-10: G43.0–G43.9
	ICD-8: 346.0–346.9
Transient cerebral ischemic attacks and related syndromes	ICD-10: G45.0–G45.9
	ICD-8: 435.0–435.9
Other inflammatory diseases of eye	ICD-10: H00.0–H01.9
	ICD-10: H10.0–H13.9
	ICD-10: H15.0–H19.9
	ICD-8: 360.0–369.9
Other diseases of the eye and adnexa	ICD-10: H02.0–H06.9
	ICD-10: H20.0–H22.9
	ICD-10: H30.0–H32.9
	ICD-10: H34.0–H36.9
	ICD-10: H43.0–H48.9
	ICD-10: H51.0–H59.9
	ICD-8: 370.0–372.9
	ICD-8: 377.0–379.9
Cataract and other disorders of lens	ICD-10: H25.0–H28.9
	ICD-8: 374.0–374.9
Retinal detachments and breaks	ICD-10: H33.0–H33.9
	ICD-8: 376.0–376.9
Glaucoma	ICD-10: H40.0–H42.9
	ICD-8: 375.0–375.9
Strabismus	ICD-10: H49.0–H50.9
	ICD-8: 373.0–373.9
Other diseases of the ear and mastoid process	ICD-10: H60.0–H62.9
	ICD-10: H65.0–H75.9
	ICD-10: H80.0–H83.9
	ICD-10: H90.0–H95.9
	ICD-8: 380.0–380.9
	ICD-8: 381.0–381.9
	ICD-8: 382.0–383.9
	ICD-8: 384.0–389.9
Acute rheumatic fever	ICD-10: I00.0–I02.9
	ICD-8: 390.0–392.9
Chronic rheumatic heart disease	ICD-10: I05.0–I09.9
	ICD-8: 393.0–398.9
Essential (primary) hypertension	ICD-10: I10.0–I15.9
	ICD-8: 400.0–404.9

(*Continued*)

Table S1 (*Continued*)

Category	ICD-codes
Angina pectoris	ICD-10: I20.0–I20.9
	ICD-8: 413.0–413.9
Acute myocardial infarction	ICD-10: I21.0–I22.9
	ICD-8: 410.0–410.9
Other ischemic heart diseases	ICD-10: I23.0–I25.9
	ICD-8: 411.0–412.9
Other ischemic heart disease	ICD-8: 414.0–414.9
Pulmonary embolism	ICD-10: I26.0–I26.9
	ICD-8: 450.0–450.9
Other heart diseases	ICD-10: I27.0–I43.9
	ICD-10: I51.0–I52.9
	ICD-8: 420.0–426.9
	ICD-8: 428.0–429.9
Conduction disorders and cardiac arrhythmias	ICD-10: I44.0–I49.9
	ICD-8: 427.0–427.9
Congestive heart failure	ICD-10: I50.0–I50.9
	ICD-8: 427.0–427.0
Intracranial hemorrhage	ICD-10: I60.0–I62.9
	ICD-8: 431.0–431.9
Cerebral infarction	ICD-10: I63.0–I63.9
	ICD-8: 432.0–434.9
Other cerebrovascular diseases	ICD-10: I64.0–I64.9
	ICD-10: I65.0–I69.9
	ICD-8: 430.0–430.9
	ICD-8: 436.0–436.9
	ICD-8: 437.0–438.9
Atherosclerosis	ICD-10: I70.0–I70.9
	ICD-8: 440.0–440.9
Other diseases of arteries, arterioles and capillaries	ICD-10: I71.0–I72.9
	ICD-10: I74.0–I74.9
	ICD-10: I77.0–I79.9
	ICD-8: 441.0–442.9
	ICD-8: 444.0–448.9
Other peripheral vascular diseases	ICD-10: I73.0–I73.9
	ICD-8: 443.0–443.9
Phlebitis, thrombophlebitis, venous embolism and thrombosis	ICD-10: I80.0–I82.9
	ICD-8: 451.0–453.9
Varicose veins of lower extremities	ICD-10: I83.0–I83.9
	ICD-8: 454.0–454.9
Hemorrhoids	ICD-10: I84.0–I84.9
	ICD-8: 455.0–455.9
Other diseases of the circulatory system	ICD-10: I85.0–I99.9
	ICD-8: 456.0–458.9
Other acute upper respiratory infections	ICD-10: J00.0–J01.9
	ICD-10: J04.0–J04.9
	ICD-10: J05.0–J06.9
	ICD-8: 460.0–461.9
	ICD-8: 464.0–465.9
Acute pharyngitis and acute tonsillitis	ICD-10: J02.0–J03.9
	ICD-8: 34.0–34.0
	ICD-8: 462.0–463.9
Influenza	ICD-10: J10.0–J11.9
	ICD-8: 470.0–474.9
Pneumonia	ICD-10: J12.0–J18.9
	ICD-8: 480.0–480.9
	ICD-8: 481.0–481.9
	ICD-8: 482.0–483.9
	ICD-8: 484.0–486.9
Acute bronchitis and acute bronchiolitis	ICD-10: J20.0–J21.9
	ICD-8: 466.0–466.9
Other diseases of the respiratory system	ICD-10: J22.0–J22.9
	ICD-10: J66.0–J99.9
	ICD-8: 510.0–514.9
	ICD-8: 517.0–517.9
	ICD-8: 519.0–519.9
Other diseases of upper respiratory tract	ICD-10: J30.0–J31.9
	ICD-10: J33.0–J34.9
	ICD-10: J36.0–J39.9
	ICD-8: 501.0–502.9
	ICD-8: 504.0–504.9
	ICD-8: 505.0–508.9
Chronic sinusitis	ICD-10: J32.0–J32.9
	ICD-8: 503.0–503.9
Chronic disease of tonsils and adenoids	ICD-10: J35.0–J35.9
	ICD-8: 500.0–500.9
Bronchitis, emphysema and other chronic obstructive pulmonary diseases	ICD-10: J40.0–J44.9
	ICD-10: J45.0–J46.9
	ICD-8: 490.0–493.9
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-10: K28.0–K28.9
	ICD-10: K30.0–K31.9
	ICD-8: 530.0–530.9
	ICD-8: 536.0–537.9
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
Diseases of appendix	ICD-10: K35.0–K38.9
	ICD-8: 540.0–543.9
Hernia	ICD-10: K40.0–K46.9
	ICD-8: 550.0–553.9
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-10: K57.0–K67.9
	ICD-10: K82.0–K83.9
	ICD-10: K87.0–K93.9
	ICD-8: 561.0–562.9
	ICD-8: 564.0–569.9
Paralytic ileus and intestinal obstruction without hernia	ICD-10: K56.0–K56.9
	ICD-8: 560.0–560.9
Other diseases of liver and gallbladder	ICD-10: K70.0–K77.9
	ICD-8: 570.0–573.9
	ICD-8: 576.0–576.9
Cholelithiasis and cholecystitis	ICD-10: K80.0–K81.9
	ICD-8: 574.0–575.9
Acute pancreatitis and other diseases of the pancreas	ICD-10: K85.0–K86.9
	ICD-8: 577.0–577.9
Infections of the skin and subcutaneous tissue	ICD-10: L00.0–L08.9
	ICD-8: 680.0–686.9
Other diseases of the skin and subcutaneous tissue	ICD-10: L10.0–L99.9
	ICD-8: 690.0–698.9
	ICD-8: 700.0–709.9

(*Continued*)

Table S1 (*Continued*)

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: 716.0–716.9
Osteoarthritis and allied conditions	ICD-10: M15.0–M19.9
	ICD-10: M47.0–M47.9
	ICD-10: M48.3–M48.3
	ICD-8: 710.0–711.9
	ICD-8: 713.0–715.9
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: M30.0–M36.9
	ICD-10: M87.0–M90.9
	ICD-10: M94.0–M99.9
	ICD-8: 730.0–730.9
	ICD-8: 733.0–734.9
	ICD-8: 738.0–738.9
Other dorsopathies	ICD-10: M40.0–M41.9
	ICD-10: M43.0–M43.5
	ICD-10: M43.7-M46.9
	ICD-10: M48.0–M48.2
	ICD-10: M48.4–M49.9
	ICD-10: M53.0–M53.9
	ICD-8: 735.0–735.9
Osteochondrosis	ICD-10: M42.0–M42.9
	ICD-10: M91.0–M93.9
	ICD-8: 722.0–722.9
Rheumatism	ICD-10: M43.6–M43.6
	ICD-10: M79.0–M79.1
	ICD-8: 717.0–718.9
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: 732.0–732.9
Soft tissue disorders	ICD-10: M61.0–M78.9
	ICD-10: M79.2–M79.5
	ICD-10: M79.7–M79.9
	ICD-8: 731.0–731.9
Osteoporosis with and without fracture	ICD-10: M80.0–M81.9
	ICD-8: 723.0–723.0
Other diseases of bone	ICD-10: M82.0–M85.9
	ICD-8: 721.0–721.9
	ICD-8: 723.0–723.9
Osteomyelitis and periostitis	ICD-10: M86.0–M86.9
	ICD-8: 720.0–720.9
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
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: 591.0–591.9
	ICD-8: 593.0–593.9
	ICD-8: 596.0–599.9
Urolithiasis/Calculus of urinary system	ICD-10: N20.0–N23.9
	ICD-8: 592.0–592.9
	ICD-8: 594.0–594.9
Cystitis	ICD-10: N30.0–N30.9
	ICD-8: 595.0–595.9
Hyperplasia of prostate	ICD-10: N40.0–N40.9
	ICD-8: 600.0–600.9
Other diseases of male genital organs	ICD-10: N41.0–N42.9
	ICD-10: N44.0–N46.9
	ICD-10: N48.0–N51.9
	ICD-8: 601.0–602.9
	ICD-8: 604.0–604.9
	ICD-8: 606.0–607.9
Hydrocele and spermatocele	ICD-10: N43.0–N43.9
	ICD-8: 603.0–603.9
Redundant prepuce, phimosis and paraphimosis	ICD-10: N47.0–N47.9
	ICD-8: 605.0–605.9
Disorders of breast	ICD-10: N60.0–N64.9
	ICD-8: 610.0–611.9
Salpingitis and oophoritis	ICD-10: N70.0–N70.9
	ICD-8: 612.0–614.9
Other inflammatory diseases of female pelvic organs	ICD-10: N71.0–N71.9
	ICD-10: N73.0–N77.9
	ICD-8: 622.0–622.9
Inflammatory disease of cervix uteri	ICD-10: N72.0–N72.9
	ICD-8: 620.0–620.9
Endometriosis	ICD-10: N80.0–N80.9
	ICD-8: 625.0–625.3
Female genital prolapse	ICD-10: N81.0–N81.9
	ICD-8: 623.0–623.9
Other disorders of genitourinary tract	ICD-10: N82.0–N82.9
	ICD-10: N84.0–N90.9
	ICD-10: N93.0–N96.9
	ICD-10: N98.0–N99.9
	ICD-8: 621.0–621.9
	ICD-8: 624.0–625.9
	ICD-8: 627.0–627.9
	ICD-8: 629.0–629.9
Other diseases of ovary, fallopian tube and parametrium	ICD-10: N83.0–N83.9
	ICD-8: 615.0–616.9
Disorders of menstruation	ICD-10: N91.0–N92.9
	ICD-8: 626.0–626.9
Female infertility	ICD-10: N97.0–N97.9
	ICD-8: 628.0–628.9
Ectopic pregnancy	ICD-10: O00.0–O00.9
	ICD-8: 631.0–631.9
Pregnancies with abortive outcome	ICD-10: O01.0–O08.9
	ICD-8: 640.0–645.9
Other complications of pregnancy or delivery	ICD-10: O10.0–O16.9
	ICD-10: O20.0–O48.9
	ICD-10: O60.0–O75.9
	ICD-10: O81.0–O99.9
	ICD-8: 630.0–639.9
	ICD-8: 651.0–666.9
	ICD-8: 670.0–678.9

(*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
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
Undescended testicle	ICD-10: Q53.0–Q53.9
	ICD-8: 752.0–752.1
Congenital deformities of hip	ICD-10: Q65.0–Q65.9
	ICD-8: 755.0–755.6
Congenital deformities of feet	ICD-10: Q66.0–Q66.9
	ICD-8: 754.0–754.9
Other congenital malformations and deformations of the musculoskeletal system	ICD-10: Q67.0–Q79.9
	ICD-8: 755.0–755.9
	ICD-8: 755.0–756.9
	ICD-8: 756.0–756.9
Other and unspecified congenital anomalies	ICD-10: Q00.0–Q04.9
	ICD-10: Q06.0–Q07.9
	ICD-10: Q10.0–Q18.9
	ICD-10: Q30.0–Q34.9
	ICD-10: Q80.0–Q99.9
	ICD-8: 740.0–740.9
	ICD-8: 743.0–745.9
	ICD-8: 748.0–748.9
	ICD-8: 757.0–759.9
Abdominal and pelvic pain	ICD-10: R10.0–R10.9
	ICD-8: 785.0–785.5
Senility	ICD-10: R54.0–R54.9
	ICD-8: 794.0–794.9

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	1.5×10^{-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

(*Continued*)

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/Calculus 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.