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Published in:
JAMA Neurology

DOI:
[10.1001/jamaneurol.2016.0022](https://doi.org/10.1001/jamaneurol.2016.0022)

Publication date:
2016

Document version
Publisher's PDF, also known as Version of record

Document license
Unspecified

Citation for published version (APA):
Egeberg, A., Hansen, P. R., Gislason, G. H., & Thyssen, J. P. (2016). Exploring the Association Between Rosacea and Parkinson Disease: A Danish Nationwide Cohort Study. *JAMA Neurology*, 73(5), 529-534. DOI: 10.1001/jamaneurol.2016.0022

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Original Investigation

Exploring the Association Between Rosacea and Parkinson Disease

A Danish Nationwide Cohort Study

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IMPORTANCE The pathogenesis of rosacea is unclear, but increased matrix metalloproteinase target tissue activity appears to play an important role. Parkinson disease and other neurodegenerative disorders also display increased matrix metalloproteinase activity that contribute to neuronal loss.

OBJECTIVE To investigate the risk of incident (new-onset) Parkinson disease in patients with rosacea.

DESIGN, SETTING, AND PARTICIPANTS A nationwide cohort study of the Danish population was conducted using individual-level linkage of administrative registers. All Danish citizens 18 years or older from January 1, 1997, to December 31, 2011 (N = 5 472 745), were included. Data analysis was conducted from June 26 to July 27, 2015.

MAIN OUTCOMES AND MEASURES The main outcome was a diagnosis of Parkinson disease. Incidence rates (IRs) per 10 000 person-years were calculated, and incidence rate ratios (IRRs) adjusted for age, sex, socioeconomic status, smoking, alcohol abuse, medication, and comorbidity were estimated by Poisson regression models.

RESULTS A total of 5 404 692 individuals were included in the reference population; of these, 22 387 individuals (9812 [43.8%] women; mean [SD] age at diagnosis, 75.9 [10.2] years) received a diagnosis of Parkinson disease during the study period and 68 053 individuals (45 712 [67.2%] women; mean age, 42.2 [16.5] years) were registered as having rosacea. The IRs of Parkinson disease per 10 000 person-years were 3.54 (95% CI, 3.49-3.59) in the reference population and 7.62 (95% CI, 6.78-8.57) in patients with rosacea. The adjusted IRR of Parkinson disease was 1.71 (95% CI, 1.52-1.92) in patients with rosacea compared with the reference population. There was a 2-fold increased risk of Parkinson disease in patients classified as having ocular rosacea (adjusted IRR, 2.03 [95% CI, 1.67-2.48]), and tetracycline therapy appeared to reduce the risk of Parkinson disease (adjusted IRR, 0.98 [95% CI, 0.97-0.99]).

CONCLUSIONS AND RELEVANCE Rosacea constitutes an independent risk factor for Parkinson disease. This association could be due to shared pathogenic mechanisms involving elevated matrix metalloproteinase activity. The clinical consequences of this association require further study.

JAMA Neurol. 2016;73(5):529-534. doi:10.1001/jamaneurol.2016.0022
Published online March 21, 2016.

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Rosacea is a common chronic inflammatory skin condition characterized primarily by transient or persistent centrofacial erythema as well as concomitant telangiectasia, papules, and pustules. However, distinct clinical patterns exist and the National Rosacea Society Expert Committee¹ recognizes 4 subtypes of rosacea that frequently overlap: (1) erythematotelangiectatic, (2) inflammatory papulopustular, (3) phymatous, and (4) ocular. Topical anti-inflammatory antibiotics, azelaic acid, or retinoids constitute the usual first-line therapies, and systemic drugs with anti-inflammatory effects, such as tetracyclines and isotretinoin, are used for moderate to severe rosacea.^{1,2}

Although the etiopathogenesis of rosacea is not fully understood, the condition has a genetic component.³ Moreover, distinct environmental triggers, including *Demodex folliculorum*, UV irradiation, temperature changes, and alcohol consumption, have been identified.¹ Rosacea skin shows an upregulation of various cytokines, in particular, antimicrobial peptides, and displays increased activation and expression of matrix metalloproteinases (MMPs).^{1,2} There is a critical interplay between MMPs and antimicrobial peptides in rosacea skin; for example, MMP-9 activates the kallikrein 5 serine protease, leading to generation of LL-37 (the cathelicidin-derived antimicrobial peptide), which may then further stimulate inflammation.¹

Matrix metalloproteinases have also been implicated⁴⁻⁶ in the pathogenesis of Parkinson disease and other neurodegenerative disorders; in experimental models of Parkinson disease, MMP-3 and MMP-9 levels are increased and contribute to dopaminergic neuronal loss. A German study⁷ of 70 patients with Parkinson disease showed that rosacea was present in 18.6% of the participants and that 31.4% reported facial flushing associated with temperature changes. In view of these data linking rosacea and Parkinson disease, we evaluated a possible association between the 2 conditions in a nationwide cohort of the Danish population between January 1, 1997, and December 31, 2011.

Methods

Data Sources and Study Population

Study approval was obtained from the Danish Data Protection Agency. Review by an ethics committee is not required for registry studies in Denmark. Conduct of this study was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology recommendations.⁸

In brief, the Danish Civil Registration System assigns a permanent and unique 10-digit personal identification number to all citizens at birth or immigration, which allows for unambiguous linkage across nationwide registries.⁹ Moreover, the Danish Civil Registration System contains information such as date of birth, sex, and vital status, and Statistics Denmark records information on tax-reported household income.¹⁰ The Danish National Patient Registry¹¹ contains information on all inpatient and outpatient (ambulatory) hospital contacts since 1978 according to the *International Classification of Diseases (ICD)* (prior to 1994 according to the 8th revision [ICD-8] and there-

Key Points

Question Do patients with rosacea have an increased risk of Parkinson disease?

Findings This population-based cohort study found a significantly increased risk of Parkinson disease in patients with rosacea compared with the general population. Notably, treatment with tetracycline was associated with a reduced risk of Parkinson disease.

Meaning Rosacea is an independent risk factor for Parkinson disease; focus on neurologic symptoms in patients with rosacea may be warranted.

after according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)*, and hospital treatment interventions, surgical procedures, and hospital-administered pharmacotherapy are coded as treatment procedure codes. All pharmacy-dispensed prescriptions in Denmark have been accurately recorded in the Register of Medicinal Product Statistics since 1994, and all drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification.¹²

All Danish citizens 18 years or older were included in the cohort on January 1, 1997, or the subsequent day that they became that age. Individuals were followed up until December 31, 2011; migration; a diagnosis of Parkinson disease; or death from any cause, whichever came first. At baseline, patients with prevalent rosacea or Parkinson disease and those with a history of anti-Parkinson dopaminergic drug use were excluded to enable accurate examination of the temporal association between exposure to rosacea and the subsequent risk of Parkinson disease. Patients with rosacea were identified by the first documentation of either a hospital (inpatient or outpatient) diagnosis of rosacea (ICD-8 code 695.3 and ICD-10 code L71) or when they obtained their second prescription of topical metronidazole (ATC D06BX01), which is the preferred first-line treatment for rosacea and is used infrequently for other skin conditions in Denmark.

End Points

The primary end point of the study was a hospital diagnosis of idiopathic Parkinson disease (ICD-10 code G20). This diagnosis has previously been validated with an accuracy of 82.4% in the Danish National Patient Register based on the criteria of the UK Parkinson Disease Society Brain Bank^{13,14} and the criteria of Gelb et al.¹⁵ Moreover, we investigated the initiation of treatment with anti-Parkinson dopaminergic agents (ATC code N04B) as a secondary end point. In a previous population-based study¹⁶ of Danish patients with Parkinson disease, 91% of the patients received these drugs, and this treatment was initiated by general practitioners in 75% of the cases on average 3 years before the patients experienced their first hospital contact for Parkinson disease.

Covariates

Stroke (ICD-8 codes 432-436 and ICD-10 codes I63-I64) was included as a covariate in the analyses, as was use of antimigraine

agents (ATC code N02C), antidepressants (ATC code N06A), and anxiolytics (ATC code N05).¹⁷⁻¹⁹ We tracked smoking history through an algorithm previously described.²⁰ Patients with a history of alcohol abuse were identified through the use of pharmacotherapy, treatment interventions, or diagnoses (eTable 1 in the Supplement). We calculated an index of socioeconomic status between 0 and 4, with 4 indicating the highest income group, based on the mean gross annual income (standardized by age) during a 5-year period before study inclusion. Baseline medication use was calculated up to 6 months and information on comorbidity, smoking history, and alcohol abuse was collected up to 5 years before the study. Information on covariates was continuously updated throughout the study period.

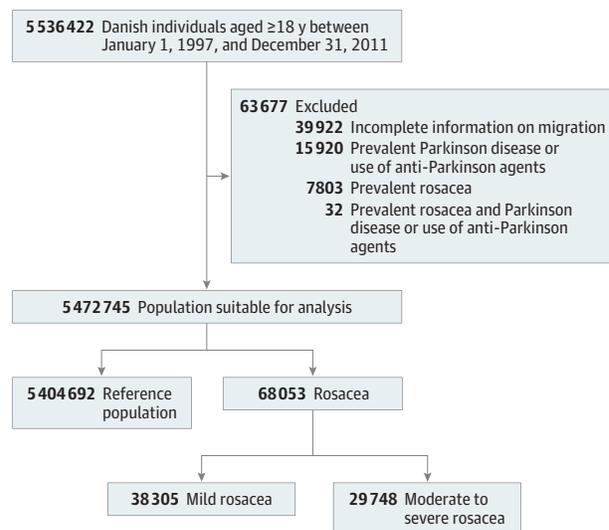
Statistical Analysis

Baseline characteristics are presented as frequencies with percentages for categorical variables and means (SDs) for continuous variables. Incidence rates were summarized per 10 000 person-years at risk. Outcomes before an index date in the rosacea group were allocated to the reference group to obtain a more accurate exposure-time allocation. For risk estimation, Poisson regression models were used to calculate crude-, age-, and sex-adjusted incidence rate ratios (IRRs), as well as IRRs adjusted for age, sex, socioeconomic status, smoking, alcohol abuse, medication, and comorbidity.

For sensitivity analyses, we retrieved information on prescriptions for tetracycline (ATC code J01A), which is the most commonly used oral prescription medication for rosacea in Denmark, to obtain a reasonably valid estimate of rosacea severity. Thus, patients were classified as having mild disease from the onset of rosacea until they fulfilled the criteria for moderate to severe rosacea (ie, initiation of oral tetracycline therapy, if appropriate). In these analyses, patients were included in the mild rosacea group until they fulfilled the criteria for moderate to severe rosacea, if appropriate. Patients were classified as having ocular rosacea if they had obtained a prescription for hypromellose eyedrops (ATC code S01XA20), which is often used to treat xerophthalmia in rosacea, and we identified patients with rhinophyma by the *ICD-10* code L71.1.

Because Parkinson disease is associated with seborrheic dermatitis, we also performed sensitivity analyses in which patients with rosacea were excluded if they had ever (ie, before, during, or after inclusion) received treatment with ketoconazole in a shampoo or topical formulation (ATC code D01AC08) or topical corticosteroids (ATC code D07A), which are the typical treatment modalities for seborrheic dermatitis in Denmark.²¹ Moreover, we repeated our primary analyses using a hospital dermatologist (inpatient or outpatient) diagnosis of rosacea (*ICD-10* code L71) as our exposure variable. Finally, to assess whether tetracycline therapy was associated with a reduced risk of Parkinson disease, we performed analyses of filled prescriptions for tetracycline regardless of the presence or absence of rosacea. Statistical significance was set at $P < .05$, and the results are reported as 95% CIs where applicable. All statistical analyses were performed with Stata, version 11.0 (StataCorp) and SAS, version 9.2 (SAS Institute Inc). Data analysis was conducted from June 26 to July 27, 2015.

Figure. Study Flowchart



Results

From January 1, 1997, to December 31, 2011, the study population comprised 5 536 422 Danish citizens 18 years or older. After excluding 7803 and 15 920 individuals with rosacea or Parkinson disease, 32 individuals with both rosacea and Parkinson disease, and 39 922 individuals with incomplete migration information, the final cohort included 5 472 745 individuals, with a maximum follow-up of 15 years. The study flowchart is shown in the Figure, and the baseline characteristics of the study population are reported in Table 1.

Risk of Parkinson Disease in Patients With Rosacea

During the study period, a total of 22 107 and 280 cases of Parkinson disease occurred among the reference population and the rosacea cohort, respectively (Table 2). Of the 22 387 individuals who received a diagnosis of Parkinson disease during the study period, 9812 (43.8%) were women, and the mean age at diagnosis was 75.9 [10.2] years. A total of 93 411 individuals in the reference population and 1169 of those in the rosacea group initiated treatment with anti-Parkinson dopaminergic agents in the 2 groups. The incidence rates of Parkinson disease per 10 000 person-years were 3.54 (95% CI, 3.49-3.59) and 7.62 (95% CI, 6.78-8.57) in the reference population and in patients with rosacea, respectively, and the incidence rates of treatment with anti-Parkinson dopaminergic agents were 15.03 (95% CI, 14.93-15.12) and 32.17 (95% CI, 30.38-34.07), respectively. Parkinson disease occurred approximately 2.4 years earlier in patients with rosacea (mean [SD] age, 73.7 [10.3] years) compared with the reference population (76.1 [10.2] years) ($P < .001$ for the difference).

The crude IRR of Parkinson disease was 2.15 (95% CI, 1.91-2.42) in patients with rosacea compared with the reference population, whereas the fully adjusted (age, sex, socioeconomic status, smoking, alcohol abuse, comorbidity, and medication) IRR was 1.71 (95% CI, 1.52-1.92), as detailed in Table 3.

Table 1. Baseline Characteristics of Study Population

| Characteristic | Population, No. (%) | |
|---------------------------------|---------------------------|----------------------|
| | Reference (n = 5 404 692) | Rosacea (n = 68 053) |
| Age, mean (SD), y | 40.8 (19.7) | 42.2 (16.5) |
| Sex | | |
| Women | 2 722 615 (50.4) | 45 712 (67.2) |
| Men | 2 682 077 (49.6) | 22 341 (32.8) |
| Socioeconomic status, mean (SD) | 2.0 (1.4) | 2.5 (1.3) |
| Smoking, ever | 406 181 (7.5) | 4644 (6.8) |
| Alcohol abuse | 76 490 (1.4) | 737 (1.1) |
| Stroke | 34 983 (0.6) | 277 (0.4) |
| Medication | | |
| Antidepressant | 152 253 (2.8) | 2137 (3.1) |
| Antimigraine | 44 604 (0.8) | 1085 (1.6) |
| Anxiolytic | 490 994 (9.1) | 6844 (10.1) |

Stratification by sex yielded similar results in fully adjusted analyses for women (IRR, 1.74; 95% CI, 1.46-2.07) and men (IRR, 1.62; 95% CI, 1.38-1.91). The adjusted IRR of treatment with anti-Parkinson dopaminergic agents was 1.59 (95% CI, 1.50-1.69) in patients with rosacea compared with the reference population and remained significant in estimates stratified for sex.

Sensitivity Analyses

In sensitivity analyses, stratification by the presumed severity of rosacea based on pharmacotherapy revealed a significantly increased risk of Parkinson disease in patients with mild rosacea (fully adjusted IRR, 1.82; 95% CI, 1.57-2.11) and moderate to severe rosacea (fully adjusted IRR, 1.84; 95% CI, 1.51-2.24)—a disease severity dose dependency was not apparent. Moreover, the fully adjusted IRRs revealed an increased risk of treatment with anti-Parkinson dopaminergic agents in mild (IRR, 1.66; 95% CI 1.53-1.79) and moderate to severe (IRR, 1.71; 95% CI, 1.56-1.88) rosacea, and the results remained similar after stratification for sex (eTable 2 in the Supplement). The fully adjusted IRRs of Parkinson disease were 1.57 (95% CI, 1.36-1.82) and 2.03 (95% CI, 1.67-2.48) for patients with rosacea who never picked up a prescription for hypromellose eyedrops and patients with presumed ocular rosacea, respectively. Among patients with rhinophyma (n = 751), there were 4 cases of Parkinson disease, and 14 patients initiated treatment with anti-Parkinson dopaminergic agents. The fully adjusted IRRs for Parkinson disease and treatment with anti-Parkinson dopaminergic agents were 1.43 (95% CI, 0.54-3.83; *P* = .50) and 2.05 (95% CI, 1.21-3.45; *P* = .007), respectively, in patients with rhinophyma. In analyses of tetracycline use (regardless of a rosacea diagnosis), filled prescriptions of tetracyclines were associated with a 2% decrease in the risk of Parkinson disease (adjusted IRR, 0.98; 95% CI, 0.97-0.99; *P* < .001).

When we excluded all patients with rosacea who had ever filled a prescription for ketoconazole (shampoo or topical formulation) or topical corticosteroids, the fully adjusted IRR of both Parkinson disease (fully adjusted IRR, 1.77; 95% CI, 1.36-2.31), and treatment with anti-Parkinson dopaminergic agents (fully adjusted IRR, 1.30; 95% CI, 1.13-1.50) remained significant. In sensitivity analyses, in which the exposure was a hospital diagnosis of rosacea, the fully adjusted IRR of Parkinson

Table 2. Incidence Rates of Parkinson Disease and Initiation of Treatment With Anti-Parkinson Dopaminergic Agents^a

| Characteristic | Population | |
|---|---------------------|---------------------|
| | Reference | Rosacea |
| Parkinson disease | | |
| No. of events | 22 107 | 280 |
| Person-years | 62 447 257 | 367 236 |
| Incidence rate (95% CI) | 3.54 (3.49-3.59) | 7.62 (6.78-8.57) |
| Treatment with anti-Parkinson dopaminergic agents | | |
| No. of events | 93 411 | 1169 |
| Person-years | 62 165 293 | 363 374 |
| Incidence rate (95% CI) | 15.03 (14.93-15.12) | 32.17 (30.38-34.07) |

^a Incidence per 10 000 person-years in the reference population and rosacea population.

disease was 2.11 (95% CI, 1.44-3.10). Similarly, when the end point was initiation of treatment with anti-Parkinson dopaminergic agents, the patients with a hospital diagnosis of rosacea had a fully adjusted IRR of 1.58 (95% CI, 1.29-1.92).

Discussion

In this nationwide study of the Danish population followed up to 15 years, we observed a significantly increased risk of new-onset Parkinson disease in patients with rosacea and a younger age at Parkinson disease onset in these individuals. The results remained consistent in fully adjusted models and in sensitivity analyses. Analyses aimed at evaluating the risk of Parkinson disease in rosacea subtypes showed a tendency toward an increased risk in patients with ocular rosacea. In addition, regardless of the presence of rosacea, a decreased risk of Parkinson disease was found in individuals who had filled prescriptions for tetracyclines.

Few risk factors for Parkinson disease have been identified; these include age, male sex, ethnicity, and certain environmental factors (eg, pesticide exposure and prior head injury [increased risk] and tobacco smoking, coffee drinking, and alcohol consumption [decreased risk]).²² Neuroinflammation is an established feature of Parkinson disease, and increased expression of MMP-3 and MMP-9 has been implicated^{4,5,23} in the loss of dopaminergic neurons and nigrostriatal pathway degeneration in mouse models of Parkinson disease in which genetic deletion of MMP-3 and MMP-9 confers significant protection. Furthermore, in an in vivo study,⁶ a polymorphism in the MMP-9 gene, which leads to higher promoter activity, was associated with a significantly increased risk of neurodegenerative disorders, including Parkinson disease. Patients with rosacea also have increased activity of MMP-1, MMP-3, and MMP-9 in affected skin regions, which leads to inflammatory tissue damage and extracellular matrix degradation.²⁴ Increased tear fluid MMP activity has also been found in patients with ocular rosacea,²⁵ and the recognition of neurogenic rosacea, a rosacea subtype that includes symptoms such as burning and stinging cutaneous pain, facial flushing, migraine, neuropsychiatric symptoms, and even tremor, lends

Table 3. Incidence Rate Ratios of Parkinson Disease and Initiation of Treatment With Anti-Parkinson Dopaminergic Agents

| Characteristic | IRR (95% CI) ^a | | |
|---|---------------------------|----------------------|-----------------------------|
| | Crude | Age and Sex Adjusted | Fully Adjusted ^b |
| Parkinson disease | | | |
| Overall | 2.15 (1.91-2.42) | 2.27 (2.01-2.55) | 1.71 (1.52-1.92) |
| Women | 1.71 (1.43-2.03) | 2.27 (1.91-2.70) | 1.74 (1.46-2.07) |
| Men | 3.15 (2.69-3.70) | 2.19 (1.87-2.57) | 1.62 (1.38-1.91) |
| Treatment with anti-Parkinson dopaminergic agents | | | |
| Overall | 2.14 (2.02-2.27) | 1.95 (1.84-2.07) | 1.59 (1.50-1.69) |
| Women | 1.58 (1.47-1.70) | 1.62 (1.50-1.74) | 1.37 (1.28-1.48) |
| Men | 3.35 (3.05-3.69) | 2.37 (2.16-2.61) | 1.79 (1.63-1.97) |

Abbreviation: IRR, incidence rate ratio.

^a All findings were significant at $P < .001$.

^b Adjusted for age, sex, socioeconomic status, smoking, alcohol abuse, comorbidity, and medication.

further support to a pathogenic link between the 2 diseases.²⁶ However, we emphasize that these findings are hypothesis generating; the basis for the pathogenic link between rosacea and Parkinson disease is unknown. Although the MMP hypothesis is intriguing, there may be other mechanisms that contribute to the observed association. For example, both rosacea and Parkinson disease have been associated^{1,27} with small intestine bacterial overgrowth and *Helicobacter pylori* infection. Notably, genetic data appear to show no link between rosacea and Parkinson disease; however, only one relatively small genome-wide association study²⁸ for rosacea has been conducted so far, to our knowledge, and *rosacea* should be regarded an umbrella term that covers several subtypes of the disease.

Tetracyclines have been used in the treatment of rosacea for decades, presumably owing to their ability to reduce kallikrein 5 serine protease activities by inhibiting MMP expression in endothelial cells and keratinocytes and thereby blocking the downstream proteolytic cleavage of cathelicidin into LL-37.^{29,30} In the present study, we found no rosacea disease severity-dependent association with the risk of Parkinson disease when moderate to severe rosacea was defined by initiation of treatment with tetracycline. Although this lack of an association could be the result of misclassification of rosacea severity, another explanation could be a neuroprotective effect of tetracycline that has been suggested both in animal models³¹ and a phase 2, randomized, double-blind clinical trial³² of treatment with a tetracycline (minocycline hydrochloride) in patients with early Parkinson disease. Indeed, in support of this assumption, we found a reduced risk of Parkinson disease in patients who had filled prescriptions for a tetracycline, and these data support a call for more definitive randomized trials of this drug class in patients with Parkinson disease.³¹ We observed an approximately 4-fold higher number of individuals treated with anti-Parkinson dopaminergic agents compared with the number of patients receiving a diagnosis of Parkinson disease. This increase is primarily explained by the fact that our primary end point was a diagnosis of idiopathic Parkinson disease, whereas these agents are also used to treat secondary parkinsonism. Typically, 4 major criteria are used for the diagnosis of Parkinson disease (bradykinesia, muscular rigidity, tremor, and postural instability), but there are various phenotypic subtypes and nonmotor features (eg, cognitive impairment, psychiatric symptoms, sleep disorders, and autonomic dysfunction).^{15,22} Indeed, it is tempting to speculate that, in patients with coexistent rosa-

cea, Parkinson disease may display other phenotypic characteristics, and it is possible that rosacea or rosacea-associated features, such as facial flushing, may contribute to support a Parkinson disease diagnosis at an early phase of the disease.

Several strengths and limitations apply to the interpretation of the present results. The Danish nationwide registries enable analysis of a vast number of individuals, thereby reducing selection bias (eg, due to age, sex, or socioeconomic status). Complete registration, as well as the prospective nature of prescription data and the ICD diagnostic codes, ensure that recall bias and bias caused by nonresponse are nearly eliminated. Continuous update of data on covariates during the study period ensured accurate registration of potential confounding factors, which could change over time. In addition, the results of sensitivity analyses add credibility to our findings. We used ICD codes and prescriptions for topical metronidazole and tetracycline for rosacea identification and severity classification, respectively. However, tetracycline is also routinely used in the treatment of acne vulgaris and some infectious diseases; nevertheless, since topical metronidazole therapy is not used for these conditions, any misclassification related to the use of a tetracycline in this specific cohort is likely negligible. In addition, minocycline is not marketed in Denmark. Misclassification was a risk in the ocular rosacea group because viscous eyedrops are used for many conditions. We attempted to rule out misclassification of rosacea and seborrheic dermatitis by excluding all patients who ever received corticosteroids or ketoconazole therapy. Notably, the sebum excretion rate is not increased in patients with rosacea, thereby nearly eliminating the possible concomitant occurrence of rosacea and seborrheic dermatitis.³³ Moreover, the observational design of our study does not allow establishment of causation, and we cannot rule out the possibility of residual confounding owing to increased exposure to medical professionals in patients with rosacea. Finally, the Danish population is primarily of Northern European descent, which may limit extrapolation to other ethnicities.

Conclusions

We observed a significantly increased risk of new-onset Parkinson disease in patients with rosacea. Further studies are needed to confirm this observation and its clinical consequences.

ARTICLE INFORMATION

Accepted for Publication: January 2, 2016.

Published Online: March 21, 2016.
doi:10.1001/jamaneurol.2016.0022.

Author Contributions: Drs Egeberg and Gislason had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Egeberg, Thyssen.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Egeberg, Hansen, Thyssen.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Egeberg, Gislason.

Obtained funding: Egeberg.

Administrative, technical, or material support: All authors.

Study supervision: All authors.

Conflict of Interest Disclosures: Dr Egeberg reported being employed by Pfizer Inc at the time of the study. Dr Gislason reported being supported by an unrestricted research scholarship from the Novo Nordisk Foundation. No other disclosures were reported.

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