

Research Article



Association between periodontal flap surgery for periodontitis and vasculogenic erectile dysfunction in Koreans

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ABSTRACT

Purpose: The National Health Insurance Service-National Sample Cohort and medical checkup data from 2002 to 2013 were used to evaluate the association between periodontal surgery for the treatment of periodontitis (PSTP) and vasculogenic erectile dysfunction (VED).

Methods: Bivariate and multivariate logistic regression analyses were applied to a longitudinal retrospective database to assess the association between PSTP and VED while adjusting for the potential confounding effects of sociodemographic factors (age, household income, insurance status, health status, residence area, and smoking status) and comorbidities (diabetes mellitus, angina pectoris, cerebral infarction, and myocardial infarction).

Results: Among the 7,148 PSTP within the 268,296 recruited subjects, the overall prevalence of VED in PSTP was 1.43% (n=102). The bivariate analysis showed that VED was significantly related to PSTP (odds ratio [OR], 1.99; 95% confidence interval [CI], 1.38–2.06; $P<0.001$), and this was confirmed in the multivariate analysis after adjusting for sociodemographic factors and comorbidities (OR, 1.29; 95% CI, 1.06–1.58; $P=0.002$).

Conclusions: Subjects with a history of periodontal flap surgery had a significantly higher risk of VED, after adjusting for potential confounding factors. Further studies are required to identify the key mechanisms underlying the association between severe periodontal disease and VED.

Keywords: Chronic periodontitis; Cohort studies; Erectile dysfunction; Periodontal diseases; Retrospective studies

INTRODUCTION

Periodontal disease (PD) is a chronic bacterial inflammatory disease [1]. In particular, severe chronic PD can affect almost every periodontal structure, including the cementum, gingiva, and periodontal ligament, and is characterized by the slow-to-rapid but irreversible progression of destruction of the supporting bone, as indicated by more than 5 mm of

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

clinical attachment loss [2]. According to the Centers for Disease Control/American Academy of Periodontology definition, the prevalence of severe PD is 1.9%, 11.7%, and 11.2% among those aged 30–34 years, 50–65 years, and 65+ years in the United States, respectively [3].

Sexual dysfunction in males refers to a persistent inability to maintain a sufficient erection or achieve sexual intercourse without an aid [4]. When such a state lasts for more than 3 months, it is generally referred to as erectile dysfunction (ED) [5]. The overall mean prevalence of ED in the United States among males aged <20, 20+, and 70+ years is 5.1% (95% confidence interval [CI], 3.8%–6.4%), 18.4% (95% CI, 16.2%–20.7%), and 70.2% (95% CI, 65.6%–74.9%), respectively, demonstrating a significant increase in prevalence with age [6].

The overall prevalence of ED in Korea was reported to be 43.3% based on the International Index of Erectile Dysfunction-5, with the prevalence rates being 23.3% and 85.8% among those aged 30–39 years and 60–69 years, respectively [7]. More than 80% of cases of ED have an organic origin (*e.g.*, vascular, neurogenic, hormonal, drug-related, and mixed etiologies), and most are caused by vasculogenic factors [8].

While PD and vasculogenic erectile dysfunction (VED) are considered inflammatory infectious diseases that share the same proinflammatory cytokines and chemokines in the vascular endothelium, controversy still exists about the presence of common pathways and mechanisms between these different diseases [9]. In addition, the results of case-control and cohort studies that have assessed the association between periodontal surgery for the treatment of periodontitis (PSTP) and VED have been ambiguous and inconsistent due to the use of vague PD definitions, small samples, and the presence of various confounding factors [10]. Therefore, based on the National Health Insurance Service-National Sample Cohort (NHIS-NSC) and medical checkup data, including smoking status, we evaluated the association between PSTP and VED by adjusting for the potential confounders of sociodemographic factors and comorbidities.

MATERIALS AND METHODS

Study design and data source

A longitudinal cohort study was conducted to assess the association between PSTP and VED in Koreans. We used a database from the NHIS-NSC produced by the Korean National Health Insurance Service Big Data Steering Department from 2002 to 2013. The Korean population in 2002 was 47.64 million, and by conducting 1,476-stage stratified sampling follow as; sex (man, woman), age (18 groups: those aged 1–79 years in 5-year intervals, and those >80 years), and household income level (41 groups: those with health insurance accounting for 20 groups each, and national health insurance beneficiaries in 0 groups). We extracted data on 1,025,340 people, who represented 2.2% of the population. The researchers were blinded to the patients' identities, and a unique random number was allocated to each individual. Subjects in the representative random population samples who died between 2002 and 2013 were automatically disqualified from inclusion in the NHIS-NSC database, while newborn representative subjects were added. Figure 1 shows a flowchart for the inclusion and exclusion of participants in the current study. We analyzed the association between PSTP and VED in the total cohort of 1,025,340 people by applying logistic regression analysis to 268,296 subjects, after excluding 429,057 subjects with no medical checkup history, female subjects (n=298,778), and male subjects younger than 20 years of age (n=29,209). The total recruited sample

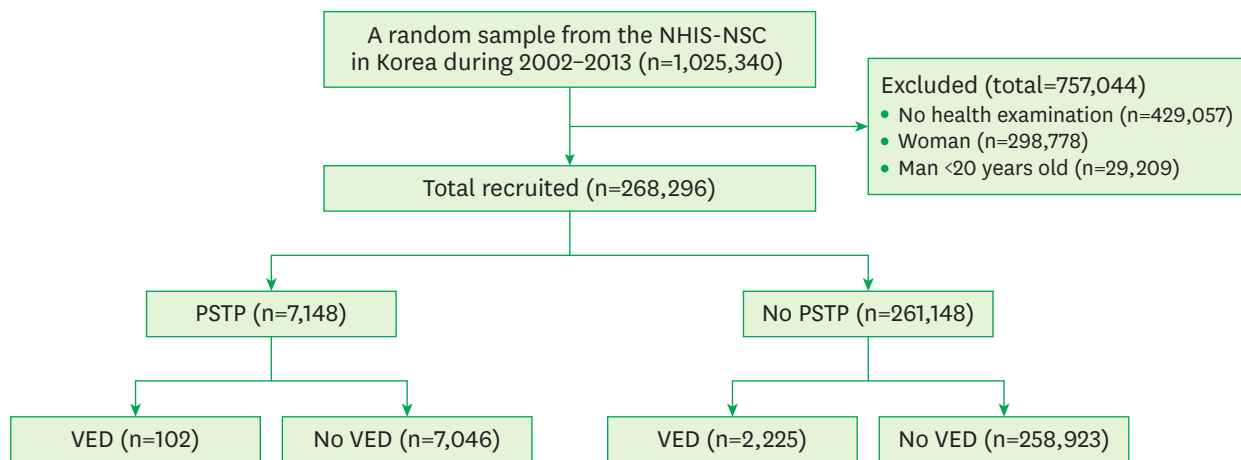


Figure 1. Flow chart of the inclusion and exclusion of participants in the NHIS-NSC from 2002 to 2013. NHIS-NSC: National Health Insurance Service-National Sample Cohort, PSTP: periodontal surgery for the treatment of periodontitis, VED: vasculogenic erectile dysfunction.

consisted of 7,148 patients who had undergone periodontal flap surgery (the PSTP group) and 261,148 control participants (the non-PSTP group). Among the 7,148 PSTP, the overall prevalence of VED PSTP was 1.43% (n=102). This study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and was approved by the Institutional Review Board of NHIS Ilsan Hospital (Approval No. 2016-03-018).

Assessment of patients treated with periodontal flap surgery

Patients who were diagnosed with PD prior to 2002 (Korean Classification of Diseases, 6th revision [KCD-6], codes K05.3 to K05.6; corresponding to the International Classification of Disease, 10th revision [ICD-10], codes K05.3 to K05.6) were excluded. Male patients older than 20 years with chronic PD (KCD-6, code K05.3; corresponding to ICD-10, code K05.3) between 2002 and 2013 were defined as PSTP if they had undergone periodontal surgery based on the following NHIS prescription codes: U1051-1052, periodontal flap operation (simple/complicated); U1071-1072, bone graft for alveolar bone defects (allogenic, xenogeneic, or substitute bone graft/autogenous bone graft); or U1081-1083, guided tissue regeneration (without bone graft/allogenic, xenogeneic, or substitute bone graft/autogenous bone graft).

Identification of patients with VED

PSTP and/or individuals diagnosed with VED prior to 2002 were washed out. Among the patients who had been treated with periodontal surgery between 2002 and 2013, those who were diagnosed with VED by a urologist at a private or general hospital were included in this cohort study.

Definition of sociodemographic factors and comorbidities

The following data regarding potential confounding sociodemographic factors were obtained from the NHIS-NSC database. Age (8 groups: those aged 20–69 years in 10-year intervals, and those aged ≥70 years), household income level (41 groups: classified into quintiles, with those in the Medical Aid Program [MAP] in the 1st quintile), insurance status (2 groups: the MAP group and the NHIS group), health status (3 groups: healthy, major disability, and minor disability based on the Handicapped Welfare Law), residence area (2 groups: rural [$<50,000$ residents] or urban [$\geq 50,000$ residents]), and smoking status were divided into smaller sub-groups and categorized using a random stratified analysis by the NHIS Big Data Steering Department.

The following comorbidities were considered to be present if they were diagnosed by a medical doctor between 2002 and 2013: diabetes mellitus (KCD-6, codes E10–E14; corresponding to ICD-10, codes E08–E13), angina pectoris (KCD-6, code I20; corresponding to ICD-10, code I20), cerebral infarction (KCD-6, code I63; corresponding to ICD-10, code I63), and myocardial infarction (KCD-6, code I21; corresponding to ICD-10, code I21).

Statistical analysis

This retrospective cohort study used the χ^2 test and logistic analyses to evaluate the association between PSTP and VED. We calculated crude and adjusted prevalence odds ratios (ORs) with 95% CIs using bivariate and multivariate logistic regression. In all assessments, a *P* value <0.05 was considered to indicate statistical significance. All statistical data were analyzed using SAS version 9.2 (SAS Institute, Cary, NC, USA) by the Department of Health Insurance Research, Ilsan Hospital, NHIS.

RESULTS

Characteristics of the study population

Those aged 20–49 years (*n*=197,536) accounted for 73.6% of the surveyed population, while 71,426 (26.6%) were in the 5th quintile of household income, 265,669 (99.1%) were in the NHIS (employees and self-employed), 257,747 (96.1%) had a good health status, 239,718 (89.3%) lived in urban areas, and 185,564 (69.2%) were smokers. Diabetes mellitus was the most common comorbidity (*n*=46,813, 17.4%), followed by angina pectoris (*n*=23,735, 8.8%), cerebral infarction (*n*=13,342, 5.0%), myocardial infarction (*n*=3,752, 1.4%), and VED (*n*=2,327, 0.9%; Table 1).

Prevalence of VED and patients treated with periodontal surgery

Table 2 presents the prevalence of PSTP and VED in the study population. PSTP corresponded to 7,148 (2.7%) of the 268,296 recruited subjects. Those aged 30–49 years (*n*=4,669) accounted for 65.4% of the PSTP, while 2,908 (40.7%) were in the 5th quintile of household income, 7,131 (99.8%) were in the NHIS (employees and self-employed), 6,951 (97.2%) had a good health status, 6,675 (93.4%) lived in urban areas, and 5,182 (72.5%) were smokers.

In addition, 2,327 patients (0.9%) were diagnosed with VED. Those aged 40–59 years (*n*=1,366) accounted for 58.7% of the VED subjects, while 864 (37.1%) were in the 5th quintile of household income, 2,312 (99.4%) were in the NHIS (employees and self-employed), 2,200 (94.5%) had a good health status, 2,056 (88.4%) lived in urban areas, and 1,505 (64.7%) were smokers.

Sociodemographic factors and comorbidities

The bivariate analysis showed that VED was significantly related to PSTP (OR, 1.99; 95% CI, 1.38–2.06; *P*<0.001). Table 3 presents the results of the multivariate logistic analysis, adjusting for sociodemographic factors and comorbidities to investigate the association between PSTP and VED. The ORs were highest in the PSTP aged 40–49 years (OR, 4.30; 95% CI, 3.90–4.75; *P*<0.001; with 20–29 years as the reference), and increased with household income (5th vs. 1st quintile: OR, 2.15; 95% CI, 1.95–2.37; *P*<0.001). NHIS (employees) showed higher ORs than those in the MAP (OR, 2.77; 95% CI, 1.70–4.51; *P*<0.001; with MAP as the reference), with the values increasing among those who were healthier and lived in an urban area. Smoking showed an OR of 1.19 (95% CI, 1.13–1.25; *P*<0.001). Cerebral infarction (OR, 1.00; 95% CI, 0.90–1.11; *P*=0.978) and myocardial infarction (OR, 0.91; 95% CI, 0.76–

Table 1. Baseline characteristics of the study population

| Characteristics | No. of subjects | Percentage (%) |
|--------------------------------|-----------------|----------------|
| Total | 268,296 | 100.0 |
| Age (yr) | | |
| 20–29 | 60,048 | 22.4 |
| 30–39 | 72,017 | 26.8 |
| 40–49 | 65,471 | 24.4 |
| 50–59 | 38,827 | 14.5 |
| 60–69 | 24,713 | 9.2 |
| ≥70 | 7,220 | 2.7 |
| Household income ^{a)} | | |
| 1st quintile | 34,189 | 12.7 |
| 2nd quintile | 42,698 | 15.9 |
| 3rd quintile | 55,309 | 20.6 |
| 4th quintile | 64,674 | 24.1 |
| 5th quintile | 71,426 | 26.6 |
| Insurance status | | |
| MAP | 2,627 | 1.0 |
| NHIS (employees) | 147,997 | 55.2 |
| NHIS (self-employed) | 117,672 | 43.9 |
| Health status ^{b)} | | |
| Healthy | 257,747 | 96.1 |
| Major disability | 2,173 | 0.8 |
| Minor disability | 8,376 | 3.1 |
| Residence area ^{c)} | | |
| Urban | 239,718 | 89.3 |
| Rural | 28,578 | 10.7 |
| Smoking | 185,564 | 69.2 |

NHIS: National Health Insurance Service, MAP: Medical Aid Program.

^{a)}Divided into 5 quintiles based on the insurance fee imposed on each household, with the MAP group classed into the 1st quintile; ^{b)}Classified based on the Handicapped Welfare Law in Korea; ^{c)}Classified using a cutoff of 50,000 residents.

Table 2. Prevalence of PSTP and VED according to sociodemographic factors

| Characteristics | Prevalence of PSTP | | | Prevalence of VED | | |
|----------------------|--------------------|-------|----------------|-------------------|-------|----------------|
| | No. | % | <i>P</i> value | No. | % | <i>P</i> value |
| Total | 7,148 | 100.0 | | 2,327 | 100.0 | |
| Age (yr) | | | <0.001 | | | <0.001 |
| 20–29 | 500 | 7.0 | | 147 | 6.3 | |
| 30–39 | 1,999 | 28.0 | | 373 | 16.0 | |
| 40–49 | 2,670 | 37.4 | | 711 | 30.6 | |
| 50–59 | 1,400 | 19.6 | | 655 | 28.1 | |
| 60–69 | 522 | 7.3 | | 401 | 17.2 | |
| ≥70 | 57 | 0.8 | | 40 | 1.7 | |
| Household income | | | <0.001 | | | <0.001 |
| 1st quintile | 525 | 7.3 | | 232 | 10.0 | |
| 2nd quintile | 790 | 11.1 | | 286 | 12.3 | |
| 3rd quintile | 1,185 | 16.6 | | 406 | 17.4 | |
| 4th quintile | 1,740 | 24.3 | | 539 | 23.2 | |
| 5th quintile | 2,908 | 40.7 | | 864 | 37.1 | |
| Insurance status | | | <0.001 | | | <0.001 |
| MAP | 17 | 0.2 | | 15 | 0.6 | |
| NHIS (employees) | 4,266 | 59.7 | | 1,184 | 50.9 | |
| NHIS (self-employed) | 2,865 | 40.1 | | 1,128 | 48.5 | |
| Health status | | | <0.001 | | | <0.001 |
| Healthy | 6,951 | 97.2 | | 2,200 | 94.5 | |
| Major disability | 23 | 0.3 | | 22 | 0.9 | |
| Minor disability | 174 | 2.5 | | 105 | 4.5 | |
| Residence area | | | <0.001 | | | <0.001 |
| Urban | 6,675 | 93.4 | | 2,056 | 88.4 | |
| Rural | 473 | 6.6 | | 271 | 11.6 | |
| Smoking | 5,182 | 72.5 | <0.001 | 1,505 | 64.7 | <0.001 |

PSTP: periodontal surgery for the treatment of periodontitis, VED: vasculogenic erectile dysfunction, MAP: Medical Aid Program, NHIS: National Health Insurance Service.

Table 3. Sociodemographic and comorbidity factors associated with PSTP in multivariate logistic regression analyses, adjusted for sociodemographic, and comorbidity factors

| Characteristics | OR | 95% CI | P value |
|-------------------------|------------|-----------|---------|
| Age (yr) | | | |
| 20–29 | 1.00 (ref) | | |
| 30–39 | 3.09 | 2.80–3.42 | <0.001 |
| 40–49 | 4.30 | 3.90–4.75 | <0.001 |
| 50–59 | 3.85 | 3.46–4.28 | <0.001 |
| 60–69 | 2.29 | 2.01–2.60 | <0.001 |
| ≥70 | 0.86 | 0.65–1.13 | 0.277 |
| Household income | | | |
| 1st quintile | 1.00 (ref) | | |
| 2nd quintile | 1.19 | 1.07–1.34 | 0.002 |
| 3rd quintile | 1.27 | 1.14–1.41 | <0.001 |
| 4th quintile | 1.49 | 1.34–1.64 | <0.001 |
| 5th quintile | 2.15 | 1.95–2.37 | <0.001 |
| Insurance status | | | |
| MAP | 1.00 (ref) | | |
| NHIS (employees) | 2.77 | 1.70–4.51 | <0.001 |
| NHIS (self-employed) | 2.14 | 1.31–3.48 | 0.002 |
| Health status | | | |
| Healthy | 1.00 (ref) | | |
| Major disability | 0.51 | 0.34–0.77 | 0.001 |
| Minor disability | 0.79 | 0.68–0.92 | 0.002 |
| Residence area | | | |
| Urban | 1.00 (ref) | | |
| Rural | 0.70 | 0.64–0.77 | <0.001 |
| Smoking | 1.19 | 1.13–1.25 | <0.001 |
| Diabetes mellitus | 1.28 | 1.21–1.36 | <0.001 |
| Angina pectoris | 1.28 | 1.19–1.38 | <0.001 |
| Cerebral infarction | 1.00 | 0.90–1.11 | 0.978 |
| Myocardial infarction | 0.91 | 0.76–1.10 | 0.335 |
| VED | 1.29 | 1.06–1.58 | 0.002 |

PSTP: periodontal surgery for the treatment of periodontitis, OR: odds ratio, CI: confidence interval, MAP: Medical Aid Program, NHIS: National Health Insurance Service, VED: vasculogenic erectile dysfunction.

1.10; $P=0.335$) were not significantly associated with PSTP. Comorbidities with significant associations were VED (OR, 1.29; 95% CI, 1.06–1.58; $P=0.002$), angina pectoris (OR, 1.28; 95% CI, 1.19–1.38; $P<0.001$), and diabetes mellitus (OR, 1.28; 95% CI, 1.21–1.36; $P<0.001$).

DISCUSSION

In the multivariate regression analysis conducted to identify risk or modifying factors in PSTP, including sociodemographic factors, smoking status, and comorbidities, the OR for VED was 1.29 (95% CI, 1.06–1.58; $P=0.002$), which was slightly higher than the ORs for diabetes mellitus (OR, 1.28; 95% CI, 1.21–1.36; $P<0.001$) and angina pectoris (OR, 1.28; 95% CI, 1.19–1.38; $P<0.001$). These results are consistent with those of Lee et al. [11], who conducted a similar analysis, adjusting for sociodemographic factors and lifestyle-related comorbidities.

In the present study, the prevalence of PSTP and VED was higher among those aged 30–49 years and those with higher incomes. This contrasts with previous studies of the prevalence of PD and VED that showed an increased prevalence among elderly subjects and those with a lower standard of living [12,13]. These discrepancies might be explained by the reduced accessibility of dental services among that population, and by the limitations of the current

study, which included only patients who visited clinics to be diagnosed and treated for severe PD and VED [14].

Periodontal pathogens such as *Porphyromonas gingivalis* cause chronic and localized inflammatory responses in periodontal tissue, and the resulting inflammatory cytokines such as C-reactive protein (CRP) and tumor necrosis factor (TNF)- α can cause systemic inflammation and endothelial dysfunction due to their circulation in the bloodstream [15]. Therefore, periodontal pathogens that chronically infect the periodontal pocket could explain the association between PSTP and systemic endothelial dysfunction [16]. VED is also intimately associated with chronic inflammation and systemic endothelial dysfunction, and CRP and TNF- α are markedly elevated in men with VED [17]. CRP and TNF- α are representative major inflammatory markers that decrease the expression of endothelial nitric oxide synthase and inhibit angiogenesis in vascular beds [18]. A gene-level analysis found associations indicating that mutual genetic factors play important pathological roles in both inflammatory diseases, with 2 linkage regions at human chromosome 9p21.3 predisposing to PD and VED [19].

Oğuz et al. [20] reported that an ED diagnosis is 3.29 times more likely in men with PD than in those with healthy gingiva, and they also found a significant positive association between the severity of PD and the prevalence of VED. Sharma et al. [21] reported that chronic PD was present in 81.8% of male patients with severe ED. Their data are supported by the strong association between PD and VED, which share the same inflammatory reaction mechanism [22]. There is evidence of inflammatory mediators such as interleukin (IL)-6, IL-8, IL-18, and TNF- α being associated with endothelial dysfunction [22]. In addition, treatment of chronic PD has been prospectively validated to reduce the risk of endothelial dysfunction at 6 months following therapy [23].

PD and VED share multiple common risk factors and pathophysiological pathways, such as older age, smoking, obesity, chronic glucocorticoid therapy, and immunological diseases [24]. Therefore, smoking cessation, reducing obesity, and avoiding other common risk factors are safe and effective means of reducing the incidence of both diseases. Some studies have also suggested that the incidence of periodontal inflammation can be reduced by taking statins (hydroxymethylglutaryl-CoA reductase inhibitors), which are the major lipid-lowering agents and one of the drugs prescribed for reducing the risk of cardiovascular disease and VED, although these results are controversial [25]. In particular, one cohort study of statins found beneficial effects in middle-aged men [26].

Zuo et al. [27] reported a mice model that included a mechanism that could be responsible for the functional impairment of penile cavernous endothelial cells via chronic low-intensity inflammation by PD. Although a healthy vascular endothelium protects against damage and exhibits anti-inflammatory and antioxidant properties, low concentrations of chronic PD-induced inflammatory cytokines and oxidative stress that accumulate in the penile endothelium can cause VED [28]. Moreover, since the penile artery has a small arterial branch, it is considered to be vulnerable to the accumulation of inflammatory products [29]. Endothelial dysfunction is the direct cause of VED, and the present study found that the OR was higher for VED than for cardiovascular disease or diabetes mellitus in PSTP [28].

Our study had several limitations. First, its observational cohort design meant that it was not possible to conclude definitively that severe PD had an adverse effect on penile erection.

Second, this study did not analyze dental records such as full probing charts or intraoral radiographs, which restricted the ability to diagnose the severity and the follow-up period of PD [30]. Third, the severity and the follow-up period of VED and other investigated comorbidities were not assessed because of insufficient medical records. Finally, the severity and follow-up status of smoking were also not assessed because of limitations in the national health examination database. Therefore, future cohort studies should be designed to assess the severity and the follow-up period of PD, smoking status, and accompanying comorbidities, including VED.

Despite these limitations, this well-controlled longitudinal cohort study that included smoking status found that PSTP was closely related to VED, as PD is known to be a risk or modifying factor for cardiovascular disease and diabetes mellitus [22]. Since PSTP have worse periodontal status than general patients with PD, the necessity of surgery seems to be more strongly associated with VED, and these patients are more likely to suffer from VED. Therefore, when a patient is diagnosed with a severe form of PD requiring periodontal flap surgery, improvement of the periodontal environment through appropriate periodontal treatment should be considered an effective intervention to reduce or reverse the prevalence of VED, including serious endothelial dysfunction.

This retrospective longitudinal cohort analysis found significant and positive associations between PSTP and the surveyed comorbidities. Our findings suggest that PSTP have a significant, but slightly higher risk of VED. Further studies are required to identify the key mechanisms underlying the association between severe PD and VED.

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