Trembling thoughts

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Oral health, orofacial pain and dysfunction in Parkinson's Disease

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“True knowledge exists in knowing that you know nothing”

“ἓν οἰδα ὁτι ουδέν οἰδα”

Socrates

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Part I

Oral health and diseases in Parkinson's disease patients

Chapter 1

Introduction

Introduction

"Disease" and "Curative approaches" have been the earlier centuries' essential focus points in medicine. However, the medical world increasingly acknowledges that quality of life is vital, in particular in the absence of a cure. A quotation from Michael J. Fox, an American actor who has been dealing with Parkinson's Disease (PD, a neurodegenerative movement disorder) for more than 30 years, disseminates this point of view in a worldwide podcasted CNN interview: "It's about getting -- being comfortable and being functioning, functional on a day-to-day basis. And that's really the thing. It's about my comfort"[1]. His "trembling" outspokenness about his disease provides more understanding of the different aspects of a hard-to-fathom illness like PD. Unfortunately, "trembling" thoughts about the disease's origin, pathophysiology, and treatment remain. Hence, it will be exactly those thoughts that motivate researchers to try and unravel this disease.

Parkinson's Disease

What we currently do know, is that PD affects the central nervous system through the loss of nigral dopaminergic neurons and the widespread accumulation of Lewy bodies, evoking motor and non-motor symptoms such as bradykinesia, tremor, pain, and cognitive deterioration[2,3]. The treatment of PD is still based on symptomatic control by means of pharmacotherapy, neurosurgery, and rehabilitation[4]. The prevalence of PD worldwide is estimated at 6.1 million people[5]. Although PD characteristics can be expressed by patients younger than 50 years, this young-onset form of PD is not that common[6]. The mean age at diagnosis is 60 years and the prevalence is increasing with age[2]. The prevalence of PD is expected to rise in the near future due to, for example, environmental factors and the ageing of our population[4,5].

Oral Health

Oral health is defined by the FDI World Dental Federation as *"(...) multi-faceted and includes the ability to speak, smile, smell, taste, touch, chew, swallow and convey a range of emotions through facial expressions with confidence and without pain, discomfort and disease of the craniofacial complex (head, face, and oral cavity)."* As such, oral health, as an umbrella term, encompasses both the functioning of the mouth and its diseases (e.g., orofacial pain and dysfunction, tooth decay, and periodontal diseases)[7]. The World Health Organization assumes that oral diseases affect almost 3.5 billion people worldwide[8]. Although, tooth decay and periodontal diseases are traditionally the primary focus points in dentistry, worldwide the most common reason to visit the dentist is orofacial pain[9]. Orofacial pain and dysfunction include both temporomandibular disorders (TMD) and bruxism[10]. TMD is an umbrella term that embraces disorders of the temporomandibular joint, masticatory muscles, and adjacent structures[11]. Symptoms of TMD include, for example, headaches attributed to TMD and orofacial pain[10]. In addition, function-related symptoms like joint sounds and limitations in jaw movements can occur as part of TMD[10]. The prevalence of TMD pain is estimated at 10% in the general adult population[12]. Although the etiology of TMD is not fully elucidated, bruxism is thought to play a role in its multifactorial etiology[13]. The bruxism definition is formulated as follows: *"... a repetitive jaw-muscle activity characterised by clenching or grinding of the teeth and/or by bracing*

or thrusting of the mandible"[14]. Furthermore, bruxism includes two circadian forms, namely awake bruxism and sleep bruxism[14,15]. The prevalence of bruxism in otherwise healthy individuals ranges between 8% and 34%, depending on, for example, the population that is studied or the methodology that is used. In a recent consensus article on the assessment of bruxism, a stepwise approach was recommended to grade the likelihood that a bruxism diagnosis is valid depending on the methodology used. First, when self-report is used, a "possible" bruxism diagnosis can be set. Second, when a clinical examination is used, supported with or without self-report, a "probable" bruxism diagnosis can be made. Third, and final, when a positive instrumental assessment is present, the bruxism diagnosis is "definite"[15].

Oral Health in PD

Because PD is most prevalent in older adults, difficulties can arise with, for example, self-care, which is essential to prevent oral diseases[7]. It has been suggested that oral health in PD patients may be worse than that in healthy controls[16]. Indeed, it has been reported that PD patients experience, for example, more tooth decay, periodontal diseases, tooth mobility, salivary problems, and impaired chewing than healthy controls[16]. However, it has been insufficiently studied to what extent oral health problems are actually associated with PD and which factors are involved in this putative association. Therefore, the general aim of this thesis was to further our knowledge on the umbrella term "oral health", including oral hygiene, oral health and diseases (e.g., gingivitis, periodontitis, tooth decay, and tooth loss), and orofacial pain and dysfunction (e.g., TMD pain, limited jaw movements, and bruxism) in patients with PD.

Content of this thesis

This thesis is divided into two parts: (i) oral health and diseases in PD patients (Chapters 2-5) and (ii) orofacial pain and dysfunction in PD patients (Chapters 6-9). **Part 1** of this thesis, which focuses on oral health and diseases in PD patients, starts off with **Chapter 2**, which is an overview of the available literature on oral health problems in PD patients and the possible associated factors. Since the oral cavity is protected by saliva, and medication can lead to a decrease in salivary flow, **Chapter 3** provides an overview of studies focussing on the measured salivary flow and the presence of subjectively experienced salivation problems in PD patients. Furthermore, we discuss the aetiological pathways for the different types of salivation problems that occur in PD patients. In **Chapter 4**, we address the question whether PD patients in The Netherlands indeed experience a lower oral health-related quality of life (OHRQoL) than healthy controls. Moreover, we aim to identify factors associated with the OHRQoL of patients with PD. Part 1 concludes with **Chapter 5,** in which we provide the results of a survey of the clinicians' view on oral health management in PD patients.

Part 2 of this thesis focusses on orofacial pain and dysfunction in PD patients. **Chapter 6** gives a broad overview of the relevant literature on orofacial pain and dysfunction in PD patients. In addition, we generate hypotheses for future research on this topic. **Chapter 7** specifically addresses the prevalence of possible TMD in a population of PD patients in the Netherlands. In **Chapter 8,** we analyse, in a population of PD patients, the prevalence of bruxism, as well as the associations

between sleep and/or awake bruxism on the one hand and dopaminergic medication and/or other factors (viz., demographic characteristics, PD-related factors, and possible consequences of bruxism) on the other hand. Besides, we present a description of a future clinical observational study protocol in **Chapter 9**, with the following primary aim: to investigate the presence of bruxism and TMD pain in PD patients through objective clinical and instrumental measurements.

Finally, in **Chapter 10,** we first briefly reflect on our studies' confirmatory and novel findings, organised per main topic (viz., oral health and diseases, and orofacial pain and dysfunction). Thereafter, we give an overview of the remaining knowledge gaps and newly raised questions after writing this thesis. We conclude the chapter with a discussion of the implications of the findings presented in this thesis for clinical practice, future research, and education.

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Chapter 2

Parkinson's disease and oral health: a systematic review

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Abstract

Background: in patients with Parkinson's Disease (PD), oral health can be affected by motor and non-motor symptoms and/or medication use.

Objective: to systematically review the literature on oral health and associated factors of oral health in PD patients.

Methods: a literature search was performed from inception up to January 20th, 2022. Included were original studies in PD patients that assessed oral health-related factors and were written in English or Dutch.

Results: 7180 articles were identified, of which 41 met the inclusion criteria (quality range poor-good). A higher prevalence of dental plaque, bleeding/gingivitis, pocket depth (³4mm), tooth mobility, caries, and number of decayed missing filled teeth/surfaces was found in PD patients than in controls. However, no difference between both groups was found when analysing edentulism and wearing dentures. Poor oral health of PD patients was associated with a longer disease duration, higher disease severity, and more prescribed medications.

Conclusions: oral health of PD patients is worse than that of healthy individuals. It is associated with the duration and severity of PD and medication use. Therefore, we advise regular appointments with oral health care professionals, with an important focus on prevention.

Keywords: Parkinson's disease, oral health, systematic review, dental caries, adult periodontitis, dental prostheses

Introduction

According to the World Health Organization, oral health is a key indicator of quality of life, overall health, and well-being of humans[1]. Approximately 3.5 billion people worldwide are affected by oral diseases, such as periodontitis and tooth decay, resulting in a poor oral health[1]. Factors like alcohol consumption, tobacco use, and an unhealthy diet (e.g., rich in carbohydrates) increase the risk of a poor oral health. In addition to lifestyle factors, also medication use can negatively influence oral health[2–6].

In the previous decades, improvement of oral health care (e.g., increased knowledge, development of new management techniques) has resulted in a lower number of edentulous patients and a higher number of older adults in high-income countries that retain their natural teeth until late in their lives[7,8]. However, because people are getting older, serious oral health problems can occur due to, for example, a decline in motor function. An example of a disease associated with worsening motor function, is Parkinson's Disease (PD). PD is a neurodegenerative disease that is neuropathologically characterised by neuronal loss in specific brain areas, such as the substantia nigra[9], and by the accumulation of the protein alpha-synuclein in Lewy Bodies[10]. Clinically, PD is characterised by both motor symptoms (e.g., bradykinesia, rigidity, tremor) and non-motor symptoms (e.g., pain, cognitive dysfunction, depression, anxiety, sleep disorders, obstipation, loss of smell)[11]. PD affects 1-4% of the adults older than 60 years of age, and its incidence increases with age[12]. To suppress the symptoms related to PD and its comorbid conditions, like nutritional and metabolic disease[13], people with PD commonly use many different types of medication (e.g., dopaminergic medication, serotonin-reuptake inhibitors, specific anti-psychotics) per day (i.e., polypharmacy)[6]. The use of such medications is crucial for the quality of life of PD patients, but can also be accompanied by side effects. In addition, people with PD may experience oral health problems, such as xerostomia or sialorrhea[14], a burning mouth sensation, periodontal disease, caries, and painful temporomandibular disorders (TMD pain)[15,16]. Consequently, these complaints can result in social distancing and worsening of the oral health-related quality of life[17].

Recently, an extensive review was published concerning the oral health in PD patients, with a focus on the role of the general and/or oral health care providers[18]. However, that review did not address factors associated with oral health problems. Therefore, the present study aimed to more extensively review the available literature on oral health problems, except for orofacial pain and dysfunction, in PD patients. In addition, the study aimed to assess the various factors associated with those oral health problems, using a professionally designed search strategy in four major databases. We hypothesised that PD patients have worse oral health than healthy individuals. In addition, we hypothesised that factors such as disease duration, disease severity, and the use of medication would be associated with worse oral health.

Material & Method

Search strategy

A literature search was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement (www.prisma-statement.org)[19]. To identify all relevant publications, we conducted systematic searches in the bibliographic databases PubMed, Embase.com, Clarivate Analytics/Web of Science (Core collection), and Wiley/Cochrane Library from inception to January 20th, 2022, in collaboration with a medical librarian. The following terms were used (including synonyms and closely related words) as index terms or free-text words: "Parkinsonian Disorders", "Oral health", "Oral functioning", and "Quality of Life". The reference lists of the identified articles were searched for relevant publications. Duplicate articles were excluded. The complete search strategies for all databases can be found in Appendix 1.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (i) inclusion of PD patients; (ii) describing oral health-related factors (except for those related to orofacial pain and dysfunction; see below, Data extraction); and (iii) written in English or Dutch language. We excluded studies based on the following criteria: (i) the full text could not be retrieved, or was not available; and (ii) certain publication types, such as legal cases, letters, editorials, interviews, and (systematic) reviews of the literature.

Study selection

Three reviewers (MV, DE, and ST) independently screened all potentially relevant titles and abstracts for eligibility. All inclusion and exclusion criteria were formulated in advance. Upon completion of the screening of all titles and abstracts, two reviewers (DE and ST) independently screened the full-text articles of the included abstracts. Through a consensus procedure with the third reviewer (MV), disagreements or doubts were resolved.

Quality assessment

One reviewer (DE) evaluated the methodological quality of the full-text papers, using the Newcastle-Ottawa Scale (NOS)[20] for cohort studies, and the Cochrane Risk of Bias Tool[21] for randomised clinical trials (RCTs) . Furthermore, the quality of the case-report studies was assessed with the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports[22]. Finally, the Appraisal tool for Cross-sectional Studies (AXIS-tool)[23] was used for cross-sectional studies, including studies with a case-control and cross-sectional design; see Appendix 2.

Data extraction

The employed search strategy yielded a wide range of oral health problems in PD patients. The present study will focus on a selection of oral health problems in PD patients (viz., oral hygiene, periodontal diseases, caries, and dental and prosthetic status) as well as on factors associated with these oral health problems. Orofacial pain and dysfunction (e.g., orofacial pain, TMD pain, burning mouth syndrome, limited jaw movements, reduced bite force, chewing difficulties, non-painful TMD,

sensory disturbances, and bruxism) in PD patients will be discussed in a separate review of the literature[24].

Two reviewers (MV and DE) extracted the following characteristics from the included articles: (1) design, (2) country, (3) sample size, (4) inclusion of control group, and (5) oral health-related factors. In addition, the following characteristics of the participating PD patients were reported: (1) gender, (2) age, (3) disease duration, (4) disease severity, and (5) medication use. The latter will be presented as either present or absent, and as the levodopa equivalent daily dosage (LEDD) (Levodopa Equivalent Daily Dosage, i.e., summation of the calculated conversion factors of each antiparkinsonian drug, aligned to 100mg immediate-release levodopa)[25]. The identified oral health-related factors were categorised in: (1) oral hygiene (2) periodontal diseases, (3) caries, and (4) dental and prosthetic status.

Analysis

All included studies were analysed using descriptive data, mainly in percentages and means, including the standard deviation. No meta-analysis could be performed due to the heterogeneous mixture of articles.

Results

Search results

The literature search generated 10315 references: 2860 in PubMed, 4695 in Embase.com, 2263 in Web of Science, and 497 in Cochrane Library. After removing duplicates, 7180 references remained. Following the study-selection procedure, 41 articles were included: 1 RCT, 3 cohort studies, 33 cross-sectional studies, and 4 case reports. The flow chart of the search and selection procedure is presented in Figure 1. The characteristics of the included studies and their participants are presented in Table 1.

Quality rating

The quality ratings for all included studies are described in Appendix 2. The quality of the cross-sectional studies (N=33) ranged between 9 and 18 points. The quality of the case-reports (N=4) ranged between 2 and 7 points. According to the criteria[22], only two case reports were of poor quality[26,27]. Finally, the quality of the articles examined by the NOS (N=3) showed that two articles had poor quality[28–31]. The majority of the included articles scored fewer points during the quality assessment because of the following reasons: (i) the methodology was not described in detail, (ii) the selection procedure was not clearly described, and/or (iii) transparency regarding non-responders was lacking. Finally, conclusions are based on articles with moderate and good quality scores; other results should be read with caution.

Oral hygiene

The results regarding oral hygiene are shown in Table 2. Twelve studies analysed the frequency of daily toothbrushing in PD patients and yielded a variety of outcomes[30,32,41,42,33–40]. Nine of these included a control group[30,33–37,39,40,41]. Three case-control studies reported a lower frequency of daily toothbrushing in PD patients compared to healthy individuals[30,37,39]. However, John et al. (2021) found no statistical difference[37], and Nakayama et al. (2004) did not perform a statistical analysis[30]. In contrast, Fukayo et al. (2003) showed significantly better brushing behaviour for PD patients than for controls[36]. Also Einarsdottir et al. (2009) found that PD patients brushed their teeth more often than controls, although no significant difference was found[34]. Only Pradeep et al. (2015) found the same brushing frequencies for both groups[40].

In total, six studies analysed the methods of daily toothbrushing in PD patients, of which three included a control group[15,33,34]. Although most PD patients still use a manual toothbrush, the study of Einarsdottir et al. (2009) showed that significantly more PD patients use an electric toothbrush than controls[34]. In addition, Verhoeff et al. (2022) found that the majority of their PD population used an electric toothbrush, however, no control group was included in that study[42].

Seven studies assessed the frequencies and methods of PD patients using interdental cleaning methods[33,34,38,40–42]. Of these, four included a control group[33,34,40,41]. No difference between PD patients and controls was reported when analysing interdental cleaning. However, the majority of PD patients did not clean interdentally. When they did, dental floss was most often reported.

Five studies assessed the self-reported difficulties that PD patients experience when performing oral hygiene[32,34,43,44,48]. Of these, two included a control group[15,34]. When analysing self-reported difficulties in performing oral hygiene, PD patients reported significantly more difficulties than controls. 15-25% of them reported to have difficulties to such extent that they needed help performing oral hygiene by another person[15,43,44].

Thirteen articles analysed the plaque percentages or indices in PD patients[7,15,29,34,35,37,38,41 45-49]. Of these, nine included a control group[7,15,34,35,37,41,45-47]. The majority of the articles showed significantly higher plaque indices, or more presence of plaque, in the PD group than in the control group[7,15,34,37,41,46]. Three studies did not find a significant difference[35,45,47]. However, the results of Bakke et al. (2011) were close to a significant difference[45], and Ribeiro et al. (2016) did report almost 25% higher mean plaque indices in PD patients than in controls[47].

In conclusion, contradictory results were found in brushing behaviour and interdental cleaning when comparing PD patients and controls. However, self-reported difficulties performing oral hygiene were consistently reported more often by PD patients than controls. Moreover, the plaque percentages or indices were higher in PD patients than controls, which indicates, despite the above, worse oral hygiene in PD patients than in controls. The quality of these articles was of varied (poor to good) quality.

Periodontal Diseases

The results regarding periodontal diseases are shown in Table 3. Eight studies described the presence or indices of bleeding in PD patients[7,15,29,30,35,38,44,50]. Of these, five included a control group[7,15,30,35,44]. Müller et al. (2011) showed a significantly higher bleeding index in PD patients compared to healthy individuals[39]. The other articles showed no significant difference in the bleeding index between PD patients and controls[15,35], or did not statistically analyse the difference[30,44].

Six studies described the presence of gingivitis[34,37,46,48,51,52], of which four included a control group[34,37,46,52]. Three studies showed a significantly higher mean gingivitis index, or presence of gingivitis, in PD patients than in controls[34,37,46]. Only one study found the same results for PD patients and healthy controls[52].

Seven articles described the presence of periodontitis in PD patients[28,31,38,46,51,53,54]. Of these, three articles included a control group[31,46,54]. Although the presence of periodontitis in a population with PD ranged between 20% and 75%, only one study showed a significantly higher presence of periodontitis in PD patients than in controls[31]. Furthermore, Frota et al. (2016) showed higher presence of periodontitis in controls than in PD patients. However, the difference in the latter study was not statistically significant different[54].

Eleven articles described periodontal pockets (³4mm) in PD patients[7,29,34,35,37,38,44,48,55-57], of which nine articles included a control group[7,34,35,37,44,48,55-57]. Five studies showed significantly more pockets or deeper pockets in PD patients than in healthy individuals[7,34,37,56,57]. Although the presence of pockets in the study of Persson et al. (1992) was higher in PD patients than in controls, they did not statistically analyse the difference between the groups[44].

In total, seven articles described the mobility of the teeth in PD patients (see Table 3)[7,15,29,37,38,50,55]. Of these, four studies included a control group[7,15,37,55] and three of these studies showed significantly more tooth mobility in PD patients than in the control group[7,15,37]. In the study by Ledwon et al., no control group was included[29]. However, the prevalence of tooth mobility was almost 100%, of which almost 20% showed severe tooth mobility[29].

In conclusion, periodontal diseases seem to be more prevalent in PD patients than in controls. Although only one article found higher bleeding indices in PD patients than in controls, gingivitis, periodontitis, pocket depth, and tooth mobility are more often reported in PD patients. The quality of the papers ranged between poor[28,29,31,34,50,57] and good[15,38,53,56].

Caries

The results regarding caries are shown in Table 4. Fifteen articles studied the presence of caries in PD patients[7,34-36,43-45,47,48,51-56]. Of these, twelve studies included a control group[7,34-36,44,45,47,48,52,54-56,]. In total, four articles found a significantly higher prevalence of caries or Decayed Missing and Filled Teeth or Surfaces (DMFT and DMFS, respectively) in PD patients than in controls[7,15,34,56]. Only two studies,

found the opposite, with controls showing a higher prevalence of caries than PD patients[36,44]. Finally, in six studies, no significant difference between the groups was found or no statistical analysis was performed[35,45,47,52,54,55]. However, the studies by Cicciù et al. (2012), Kennedy et al. (1994), Bakke et al. (2011) and Frota et al. (2016) did find higher frequencies of caries in PD patients[45,52,54,55].

In conclusion, caries is more often observed in PD patients than in controls. The quality of the articles that included a control group were of moderate to good quality.

Dental and prosthetic status

The results regarding dental and prosthetic status are shown in Table 5. The number of present or missing teeth in PD patients was described in fourteen articles[28,29,34,38,39,44,45,48,49,54-56,58,59], of which nine included a control group[34,39,44,45,48,54-56,59]. Two studies described a significantly higher mean number of missing teeth or present teeth[34,56]. Although three studies showed no significant difference between the two groups[39,44,45], the study of van Stiphout et al. (2018) did find that PD patients showed a higher number of root remnants than controls[15]. In contrast, the study by Frota et al. (2016) found the opposite. However, no exact numbers of missing teeth were described in the latter study[54].

Edentulous PD patients were described in fifteen articles[30,33,42-45,48,50,54,56,58-62,]. Of these, eight studies included a control group[33,44,45,48,54,56,59,62]. They did not show significant differences in being edentulous or wearing (partial) dentures between PD patients and the control group. Although both groups had similar frequencies of wearing dentures, Nakayama et al. (2004) reported that PD patients complained more about denture discomfort than controls (OR 3.9 95% CI 1.9-8.0)[30]. Besides, Frota et al. (2016) reported a higher frequency of self-reported unsatisfactory stability of the prosthesis in PD patients (85.7%) than in controls (54.5%)[54]. Furthermore, Bakke et al. (2011) showed that 40% of the PD patients wore fixed or removable prostheses, compared to 27% in the control group[45]. However, Bakke et al. (2011) did not perform a statistical analysis[45].

In total, six articles dealt with implant treatment for prosthetic needs in PD patients (Tables 5 and 6)[27,33,45,63,64,65]. Two of these employed a case-control design (Table 5), while four were case studies (Table 6). Baumann et al. (2020) analysed the difference in frequencies of fixed dentures between PD patients and controls[33]. However, there was no significant difference between the two groups[33]. Bakke et al. (2011) found higher numbers of fixed or removable dentures in PD patients compared to controls[45]. However, no statistical analysis was performed[45]. In the four articles that reported cases, all patients were treated with implants (viz., fixed dentures or denture stabilization using non-rigid telescopic copings on implants)[27,63,64,65]. The technical details are reported in Table 6. Three of the four case reports concluded that improvement in, for example, function, food selection, quality of life, and chewing ability occurred after reconstruction[27,63,64]. Finally, in a case series of nine PD patients, Packer et al. (2009) described their implant-based prosthetic treatment[65]. Before implant surgery, all patients had problems with controlling their complete or partial removable dentures. However, after treatment, patients showed a significant difference in satisfaction, eating, and oral well-being. In addition, a significant improvement in the quality of life was seen at 3-month and 12-month (post)-treatment[65].

In conclusion, most of the studies did not find a significant difference in being edentulous, presence of partial removable dentures, or presence of complete dentures between PD patients and the control group. Six of the papers were of poor quality[28–30,43,50,61].

Factors associated with oral health in PD

The results regarding factors that are associated with oral health problems in PD patients are shown in Table 7. Thirteen studies analysed whether such factors could be identified[7,15,29,37,38,40,41,43-46,49,56]. Of them, four studies analysed whether gender is associated with oral health problems in PD patients[7,37,38,41]. Only one study found a significantly higher prevalence of caries lesions in males than in females[7]. However, this study also reported that males had a higher mean disease severity than females[7]. The other articles did not find a significant gender difference in caries lesions. However, they did report lower frequencies of tooth brushing in males, and higher frequencies of gingivitis, oral hygiene index, pocket depth, missing teeth, and severe tooth loss[37,39,58].

Five studies analysed whether a longer disease duration is associated with more oral health problems in PD patients[15,37,43,45,56]. One study found significantly more chewing problems, and increased number of teeth with restorations, and a higher tooth mobility grade with an increasing duration of the disease[15]. John et al. (2021) did not report statistical differences[37]. However, the oral healthy index, gingivitis index, and pocket depths showed higher scores when the duration of the disease was longer than three years. Bakke et al. (2011) found a lower number of teeth when the disease duration was longer[45]. However, no statistical difference was found.

Ten studies analysed whether increased disease severity (including motor and non-motor symptoms) is associated with oral health problems[15,29,37,38,40,43,44,45,49,56]. With the exception of a single study[43], all studies found significantly worse oral health (viz., poorer oral hygiene index, lower number of teeth, more caries lesions, higher gingivitis and plaque index, more bleeding on probing, more pockets, difficulty performing oral hygiene, and chewing and biting difficulties) when disease severity was worse.

Four articles analysed whether oral health problems are associated with medication use[29,41,46,56]. An association was reported in two articles. Barbe et al. (2017) found that the gingivitis index was higher when the prescribed number of medications was higher, which indicates a negative association between gingivitis and the number of prescribed medications[46]. Besides, Rozas et al. (2021) found that patients using levodopa/carbidopa had significantly different oral microbiota than PD patients that were not using this specific anti-parkinsonian medication[41]. Although Ledwon et al. (2020) did find worse plaque indices when the number of medications was higher, no statistical difference was found ($p=0.06$)[29]. Only Hanaoka et al. (2009) did analyse if a correlation exists with the dosage of prescribed dopaminergic medication and oral health; however no such correlation was found[56].

Although the results are contradictory, male gender, a longer disease duration, worse disease severity, and the number of prescribed medications are associated with worse oral health. Only two articles were of poor quality[29,43]: Anastassiadou et al. (2022) did not find associations, however, Ledwon et al.

(2020) did find an association with higher plaque indices when disease severity increases[29,43]. The latter finding was in agreement with other studies that were of moderate to good quality.

Discussion

This study aimed to provide a comprehensive review of the available literature on oral health in PD, and to evaluate factors associated with oral health problems. In total, 41 studies were included. The majority of the studies indicate that oral health is worse in PD patients than in healthy controls. Only the prevalence of being edentulous or wearing complete dentures did not differ between PD patients and healthy controls. The thirteen studies that analysed factors associated with oral health problems in PD show that gender, disease duration and severity, and medication use could be associated with worse oral health in PD patients.

Recently, a review by Auffret et al. (2021) was published on oral health in PD patients. However, their review did not include oral health-related factors. The current review used an extensive search strategy in four major databases, which yielded a larger number of relevant articles (N=41) compared to Auffret et al. (2021)(N=25). Only three articles that were included by Auffret et al. (2021) were excluded in the current review, because of those articles' study design (e.g., review)[66] and outcome measure (viz., treatment strategy instead of oral health-related factors)[67,68]. It should be noted that the conclusions about oral health in PD patients did not differ between the two reviews; nevertheless, the current review supports the earlier findings with a higher reliability because of the more comprehensive search strategy and included quality assessment. Furthermore, our conclusions are also based on factors associated with oral health-related problems in PD patients.

Oral hygiene

Only two articles reported significantly different oral hygiene frequencies in PD patients compared to healthy individuals[36,39]. Müller et al. (2011) found significantly lower frequencies of daily toothbrushing in PD patients compared to the control group. In contrast, Fukayo et al. (2003) showed significantly more daily toothbrushing in the PD population than in the control group. The difference is that their PD group visited the university hospital for dental treatment, while the control group visited the regular dental clinic. Therefore, the possibility exists that the PD group may have been more conscious of their oral health than the control group. However, it is also possible that PD patients received more help from caregivers regarding their oral health. Although the latter was not reported, Fukayo et al. (2003) also showed a lower DMFT in PD patients compared to healthy controls. Furthermore, John et al. (2021) and Nakayama et al. (2004) support the findings of Müller et al. (2011) of lower frequencies in PD patients than in healthy people, albeit not significantly different. All other nine articles on this topic reported no difference between the two groups[30,33–37,39-41]. This is in contrast with the other results reported in this review, showing higher presence of plaque, bleeding, gingivitis, periodontitis, and deeper pocket-depth in PD patients compared to controls. An explanation could be that although PD patients may not perform oral hygiene less often, they had difficulties with toothbrushing and plaque removal because of the motor and non-motor symptoms. This notion is supported by studies

reporting an association between oral health-related diseases and longer disease duration or severity of motor and/or non-motor symptoms[15,37,38,56,69]. Van Stiphout et al. (2018), Persson et al. (1992), and Anastassiadou et al. (2002) did show that PD patients reported a higher need for help performing oral hygiene than the control group.

The higher prevalence of oral health-related diseases in PD patients suggests that more focus should be put on prevention. Oral health care providers should be aware that PD patients cannot always brush their teeth as thoroughly as needed, and that individualised help (e.g., help from caregivers, frequent visits to a dental hygienists) should be recommended.

Periodontal diseases and caries

The results of this systematic review suggest that periodontitis is more prevalent in PD patients than controls. Periodontal disease is one of the most prevalent chronic inflammatory diseases of the oral cavity, affecting the teeth' supporting tissues[70]. It is known that poor oral health behaviours can trigger the onset and progression of periodontal disease[38]. Furthermore, periodontitis is recognized as polymicrobial, though gram-negative bacteria play a significant pathogenic role[29]. These periodontal bacteria fabricate endotoxins, thus increasing the inflammatory burden and increasing inflammatory biomarkers (e.g., IL-1, IL-6, TNF-x, C-reactive proteins, and reactive oxygen species)[29]. An increase in the production of inflammatory biomarkers is hypothesised to be associated with dopaminergic neuronal cell damage or apoptosis[29,31,38]. According to this hypothesis inflammatory biomarkers can enter the bloodstream and cause a systemic inflammatory response, subsequently leading to neuronal cell damage[71]. Although the blood-brain barrier normally prevents entry of substances into the brain, suggestions are made that in some circumstances (e.g., entry through fenestrated capillaries near the base of the brain), this can happen[71]. In this way, an imbalance of periodontitis and inflammatory factors might be a causative factor in systemic disease. Obviously, this hypothesis needs to be corroborated in future research.

Changes in the bacterial flora of the oropharynx, host resistance, and impaired pulmonary function are important factors that can increase the risk of aspiration pneumonia[53]. In PD, dysfunctional swallowing (i.e., dysphagia) is a common symptom that can lead to aspiration of oropharyngeal secretions and materials (viz., liquids, food), which predisposes to aspiration pneumonia[53,72]. Taken together, the higher prevalence of periodontitis and caries in PD patients, which results in a changed bacterial flora, in combination with dysphagia, may explain the 2-4 times higher chance of aspiration pneumonia, with the risk of hospitalisation and even death[73]. Indeed, treatment of caries appears to be a protective factor against aspiration pneumonia[53]. Maintaining good oral health and regular control of the oral biofilm reportedly reduce the number of respiratory pathogens, thereby reducing the risk of aspiration pneumonia and ultimately death in PD patients[53].

Finally, in the study of Einarsdóttir et al. (2009), a higher amount/ml of Streptococcus mutans was found in stimulated whole salivary flow rate in PD patients ($7.4x10^5$) compared to controls ($5.8x10^5$) ($p<0.03$). Also lactobacillus was found to be more prevalent in whole salivary flow of PD patients ($7.0x10^4$) than in that of controls ($4.3x10^4$)($p<0.01$)[34]. This could explain the higher prevalence of

caries in PD patients. So, not only worse oral hygiene but also the composition of the oral biofilm may be altered, suggesting a higher risk of caries.

Dental and prosthetic status

The results of this systematic review suggest that PD patients do not differ from controls, regarding the number of teeth present. At first sight, this might seem contradictory with the other results, demonstrating worse oral health in PD patients than in controls. A possible explanation could be that PD patients avoid dental visits, resulting in the same number of teeth, yet with more dental problems. Van Stiphout et al. (2018) showed, for example, a significantly higher number of root remnants in PD patients than in controls. Alternatively, this result could also be explained by the fact that dental treatments are probably harder to perform in PD patients than in healthy controls, resulting in a worse prognosis of restorations or teeth.

Few studies showed a difference in the presence of a (partial) denture in PD patients compared to healthy controls. After placing partial removable conventional dentures, a significant decrease of 76% in total Oral Health Impact Profile-49 scores was found($p<0.05$). This indicates that PD patients experience improvements in oral health and therefore a higher quality of life[59]. Nevertheless, PD patients experienced their dental prosthesis as less comfortable than healthy controls[30]. This could be explained by their reduced motor control. Therefore, it is highly recommended to prevent PD patients from becoming edentulous and to avoid making (conventional) dentures. However, when necessary, a good fitting (conventional) denture, did improve the OHRQoL and is therefore a good treatment option in PD patients. Furthermore, implant-supported overdentures in PD patients might be a solution, although the results of the studies on this topic should be interpreted with caution because of their poor quality.

Associated factors with oral health in PD

The results of this review suggest that in PD patients, males have a higher risk of developing periodontal diseases, caries, and pneumonia than females. This is in line with the findings in the literature in healthy adults[74]. These results might be due to worse self-care and less dental visits in males than in females. Besides, men are more likely to ignore their oral health[75].

Our review shows that the duration and the severity of PD are associated with worse oral health. It would appear that when the severity of PD increases and cognitive function deteriorates, the number of untreated caries lesions increases. Possibly, conservative dental treatment by dentists is complex in this category of patients. Therefore, it seems important to avoid conventional dental treatment in PD patients, while focusing on prevention could be crucial.

Only some articles analysed whether an association was present between the use of medication and oral health-related diseases. The results imply that such an association exists, however, conclusions should be drawn with caution because of the limited number articles and the poor to moderate methodology. The polypharmacy in PD patients may cause salivary hypofunction[14]. An objectively

reduced level of saliva carries higher risks for the oral environment. However, many PD patients suffer from drooling[14]. A recent scoping review showed that although subjective drooling complaints are more frequent in PD patients than in controls, objective salivary flow may yet be reduced. None of the included articles showed a higher salivary flow rate in PD patients than in controls. We concluded that salivary problems in PD patients are complex of nature[14].

Limitations of the study and further recommendations

This study has several limitations. First, the included studies used different methodologies and outcome measures. Therefore, a meta-analysis could not be performed, and the results should thus be interpreted with caution. Second, the design of the included studies was mainly cross-sectional. Therefore, we recommend that longitudinal studies should be designed and that researchers consider to include disease duration, disease severity (including motor and non-motor symptoms), and medication use. Third, in most of the included studies PD patients in early disease stages and with relatively low disease severity, were included. In spite of this bias, a difference was already observed in this group of patients compared to healthy controls. Therefore, we hypothesize that when disease duration of PD patients is longer and the severity of the motor complaints is more severe, oral health problems will become even worse. Finally, there is a gap in the literature about the success rate of implants in PD patients. Because of the suggested risks of failure when horizontal movements (e.g., due to dyskinesias or bruxism) occur, clinicians may possibly be reluctant to treat PD patients with implants. In spite of the poor quality of the included papers on implant therapy in PD patients, they all reported positive effects of the therapy on quality of life and satisfaction. Moreover, the impact of horizontal movement in implant failure is recently under discussion[76,77]. Therefore, we recommended studying the possibilities of this treatment option in PD, to improve the quality of life of PD patients.

Clinical relevance

The oral environment influences the oral health-related quality of life [17]. Moreover, oral health can have an impact on general health in several ways[17]. In a population of PD patients, some general health problems are already known (e.g., weight loss, cognitive decline). When oral health becomes more difficult to manage, an elevated risk for weight loss and cognitive decline could occur[78]. This systematic review demonstrates that the oral health of PD patients is worse than that of healthy controls. Therefore, oral health care providers should be aware of the risks and be able to explain the consequences of reduced oral health to PD patients and their caregivers. When aware of the consequences, patients may become more eager to prevent the risks. Preventive measures could help postpone conservative treatment, with the advantage of avoiding treatments that are difficult for both oral health care providers and PD patients. Although this patient group is still a minority, the expected prevalence is increasing[12]. Thus, dentists will likely treat more PD patients in the future.

Conclusion

This systematic review showed that oral health in PD patients is worse than in healthy controls. Specifically, oral hygiene, periodontal health, and caries prevalence was worse in PD patients than in healthy controls. For the dental and prosthetic status, no difference was found. Limited data is available on factors associated with the health of the oral environment. Although oral health is probably subordinate to other PD symptoms, it is positively associated with the oral health-related quality of life and systemic diseases. Therefore, we strongly advise regular appointments with oral health care providers and the rigorous implementation of preventive strategies. Furthermore, we recommend a interdisciplinary approach, to overcome difficulties during prevention strategies and dental treatments.

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Figures and tables

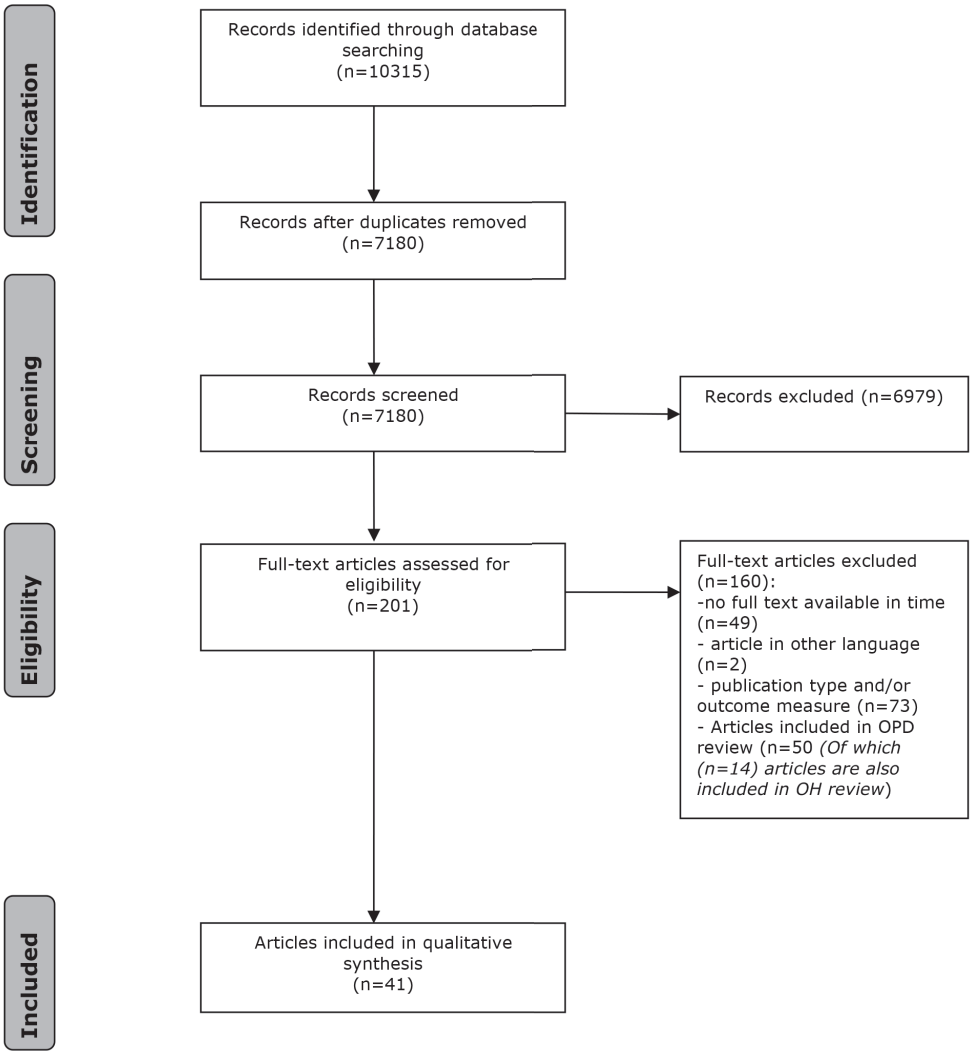

Figure 1: Flowchart of the search and selection procedure of studies.

Table 1. Characteristics and demographics of the included studies (N=31) and participants (N=10.533).

Article	Design	Country	Np[1]	Nc	Male gender PD [N (%)]	Age PD [M±SD]
Anastassiadou et al., 2002	CS	Greece	51	-	32 (63%)	67.5±2.8
Bakke et al., 2011	CS	Denmark	15	15	6 (40%)	*61.0-82.0*
Baram et al., 2020	RCT	Denmark	29		15 (51%)	32-72
Barbe et al., 2016	CS	Germany	100	-	72 (72%)	71±8.7
Barbe et al., 2017 [1]	CS	Germany	26	26	14 (54%)	69.0±9.0
Barbe et al., 2017 [2]	CS	Germany	30	30	17 (56.7%)	69.3±8.0
Baumann et al., 2020	CS	Hungary	35	42	32	62.9±9.8
Bonefant et al., 2016	CS	Canada & France	198^	-	105	69.0±10.3 68.2±9.6
Botelho et al., 2020	RCH	USA	37	-	27 (41%)	58.3±?
Chang et al., 2016	CH	Taiwan	2001^	-	1031 (51%)	74.78±7.46 70.16±9.17
Chen et al., 2018	CS	Taiwan	4765	19060	2359 (50%)	40.0(>)70.0
Chu et al., 2004	CR	China	1	-	0 (0%)	83.0±?
Cicciù et al., 2012	CS	Italy	45	45	17 (38%)	65.0-78.0
Clifford et al., 1995	CS	Ireland	228	-	121 (53%)	69.5#
Clifford et al., 1998	CS	Ireland	115	-	65 (57%)	70.0±?
Einarsdóttir et al., 2009	CS	Iceland	67	55	39 (58%)	(<)60.0 (>)70.0
Fleury et al., 2021	CS	Switzerland	20	20	9 (45%)	62.8
Frota et al., 2016	CS	Brazil	35	20	?	71.3±?
Fukayo et al., 2003	CS	Japan	31	104	17 (55%)	60.0(>)70.0
Gopalakrishnan et al., 2021	CS	India	50	-	41 (82%)	30-60
Hanaoka et al., 2009	CS	Japan	89	68	38 (43%)	71.2±5.5
Heckmann et al., 2000	CR	Germany	3	-	2 (66%)	75.7±?
John et al., 2021	CS	India	32	42	18 (56.3%)	58.4±10.6
Kennedy et al., 1994	CS	USA	28^	14	16 (57%)	1 65.7±6.2 2 67.6±9.2
Ledwon et al., 2020	CH	Austria	61	32	55 (59%)	70.8±8.4
Liu et al., 2015	CR	Taiwan	1	-	1 (100%)	76.0±?
Lyra et al., 2020	CS	Portugal	28	-	23 (82%)	72.3±8.1
Lyra et al., 2021	CS	Portugal	214	-	107(50%)	66.3±15.6
Müller et al., 2011	CS	Germany	101	75	55 (54%)	66.2±10.5
Nakayama et al., 2004	CS	Japan	104	191	44 (42%)	>60.0±?
Packer et al., 2009	CS	UK	9	-	9 (100%)	63.0±?
Packer et al., 2015	CR	UK	4	-	?	?
Persson et al., 1992	CS	Sweden	30	585	17 (57%)	73.0±7.3
Pradeep et al., 2015	CS	India	45	46	30 (67%)	54.5±9.1

Disease stage HY [M ± SD]	Disease severity MDS UPDRS-III [M ± SD]	Disease duration in years [M ± SD]	APM [Y/N]	LEDD (mg/day ±SD)	Oral health factor(s)	Associated factors
2.6±0.9	?	10.1 ± 5.4	?	?	OH; CAR; DP	DD; DS
2-4	?	6.7 ± 3.8	Y	?	OH; CAR; DP	DD; DS
2.9±0.4	20.6±4.9	11.7 ± 5.0	?	?	OH; DP	DS
?	17.5±8.6	?	Y	820±541.8	OH	DD
?	13.0±9.0*	9.0±4.0	Y	680±385	OH; P	Med
?	12.0±8.8	?	Y	661±376.7	OH; P	-
?	?	?	?	?	OH; DP	-
2.5-3 #	?	6-10 #	Y	630.1 ±? [1] 653.9 ±? [2]	DP	-
?	?	?	Y	?	P; DP	-
?	?	?	Y	?	P; CAR	-
?	?	?	?	?	P	-
?	?	0.33	Y	?	DP	-
1-2	?	?	?	?	P; CAR; DP;	-
?	?	?	?	?	P; DP	-
?	?	?	Y	?	DP;	-
?	?	?	?	?	OH; P; CAR; DP	-
2	15	4.7	Y	522.5±?	OH; P; CAR	-
?	?	?	?	?	C; P; DP;	-
1-3	?	5.9 ± 5.0	Y	?	OH; P; CAR	-
?	?	?	?	?	P; CAR	-
?	?	?	Y	453 ± 232	P; CAR; DP	DD; DS; Med
3.0	?	4.3	?	?	P; DP;	-
?	?	?	?	?	OH; P	G; DD; DS
3.1 ± 0.77 [1] 2.9±0.83 [2]	?	8.6 ± 5.0 [1] 9.4 ± 5.5 [2]	Y	?	P; CAR; DP;	-
?	20.0±?*	>3.0	Y	?	OH; P; DP	DS; Med
64.3%	?	14.0	?	?	DP	-
2.7	?	?	Y	?	OH; P; DP	G; DS
?	?	?	Y	?	DP	G; DS
3-5	30.6 ± 13.8	?	?	?	OH; P; CAR; DP;	G
?	?	?	?	?	OH; P; DP	-
?	?	?	?	?	DP	-
?	?	>10	?	?	DP	-
?	?	11 ± 5.4	Y	?	OH; P; DP; CAR	DS
?	?	?	?	?	OH; P	DS

Article	Design	Country	Np[1]	Nc	Male gender PD [N (%)]	Age PD [M±SD]
Ribeiro et al., 2016	CS	Brazil	17	20	9 (53%)	69.41±4.65
Ribeiro et al., 2017 [1]	CS	Brazil	17	20	9 (53%)	69.41±4.65
Ribeiro et al., 2017 [2]	CS	Brazil	17	17	9 (53%)	69.41±4.7
Rozas et al., 2021	CS	USA	30	30	47(63%)	69.2±9.4
Schwarz et al., 2006	CS	Germany	70	85	39 (56%)	64.5±?
Van Stiphout et al., 2018	CS	Netherlands	74	74	48 (65%)	70.2±8.8
Verhoeff et al., 2022	CS	Netherlands	341	411	60 (17.6%)	65.5±8.4

Note| ? = unknown, RCT=randomized controlled trial, CS=cross-sectional, CH=cohort study, RCH= retrospective cohort study, CR=case report, USA = United States of America, UK= United Kingdom, NL= The Netherlands, Np= Number of PD patients, Nc= Number of controls, PD= Parkinson's Disease; N=Number, %=Percentage, SD= standard deviation, M=Mean, HY=Hoehn & Yahr scale, MDS-UPDRS-III = Movement Disorders Society Unified Parkinson Disease Rating Scale part three*=UPDRS-II, APM= Anti-parkinsonian medication, Y=Yes, N=No, LEDD=Levodopa Equivalent Daily Dosage, OH= oral hygiene (viz., frequency and method of toothbrushing, interdental cleaning, difficulties performing oral hygiene and plaque), P= periodontal diseases (viz., bleeding, gingivitis, pocket depth, mobility and periodontitis), CAR = caries; DP = dental and prosthetic

Disease stage HY [M ± SD]	Disease severity MDS UPDRS-III [M ± SD]	Disease duration in years [M ± SD]	APM [Y/N]	LEDD (mg/day ±SD)	Oral health factor(s)	Associated factors
?	?	6.76±3.80	Y	?	OH; CAR; DP	-
?	?	6.76±3.80	Y	?	OH; DP	-
?	?	6.76±3.80	Y	?	DP	-
?	?	?	Y	?	OH	G; Med
?	?	?	Y	?	P	-
2.4	?	?	?	?	OH; P; CAR; DP	DD; DS
?	11.5 ± 7.5	7.0±5.5	?	?	OH; DP	-

Table 2. Results of oral hygiene (viz., frequency of daily toothbrushing, methods of toothbrushing, individuals using interdental cleaning means, self-reported difficulties performing oral hygiene, and presence of plaque) in PD patients compared to controls.

Oral Hygiene			
	Frequency of daily toothbrushing		
Article	**PD**	**Control**	**p-value**
Barbe et al., 2016	78% ≥ 2x per day	N/A	N/A
Baumann et al. 2020	62.8% ≥ 2x per day	69% ≥ 2x per day	N/A
Einarsdóttir et al., 2009	72% 2x per day	55% 2x per day	p=0.08
Fleury et al., 2021	100% ≥ 1x per day	100%≥ 1x per day	NS
Fukayo et al., 2003	2.8±0.2 per day	2.1±0.1 per day	**p≤0.01**
John et al., 2021	28.1% 2x per day	50% 2x per day	NS
Lyra et al., 2020	67.9% ≥ 2x per day	N/A	N/A
Müller et al., 2011	1.7±0.8 per day	2.1±0.8 per day	**p≤0.01**
Nakayama et al., 2004	28% not every day	0% not every day	N/A
Pradeep et al., 2015	76% more than once	76% more than once	N/A
Rozas et al., 2021	60%≥ 2x per day	73%≥ 2x per day	P=0.27
Verhoeff et al., 2022	72.7% ≥ 2x per day	N/A	N/A
	Method of daily toothbrushing		
Article	**PD**	**Control**	**p-value**
Barbe et al., 2016	43% electric toothbrush	N/A	N/A
Einarsdóttir et al., 2009	31% electric toothbrush	12% electric toothbrush	**p≤0.05**
Lyra et al., 2020	25% electric toothbrush	N/A	N/A
Baumann et al. 2020	22.9% electric toothbrush	21.4% electric toothbrush	N/A
Van Stiphout et al., 2018	48.6% electric toothbrush	40.5% electric toothbrush	p=0.40
Verhoeff et al., 2022	78% electric toothbrush	N/A	N/A
	Individuals using interdental cleaning methods		
Article	**PD**	**Control**	**p-value**
Barbe et al., 2016	No interdental cleaning	N/A	N/A
Baumann et al. 2020	8.6%	9.5%	N/A
Einarsdóttir et al., 2009	51% dental floss	41% dental floss	0.30
Lyra et al., 2020	39%	N/A	N/A
Pradeep et al., 2015	13% dental floss	20% dental floss	N/A
Rozas et al., 2021	47% dental floss	50% dental floss	P=0.80
Verhoeff et al., 2022	39% ≥ 1x per day	N/A	N/A
	43.2% interdental brushes (metal)	N/A	N/A

Self-reported difficulties oral hygiene			
Article	**PD**	**Control**	**p-value**
Anastassiadou et al., 2002	57%	N/A	N/A
	12% needed help	N/A	N/A
Barbe et al., 2016	29%	N/A	N/A
Einarsdóttir et al., 2009	3%	0%	0.20
Persson et al., 1992	47%	N/A	N/A
	13% needed help	N/A	N/A
Van Stiphout et al., 2018	15% needed help	1% needed help	**p≤0.01**
Presence of plaque			
Article	**PD**	**Control**	**p-value**
Einarsdóttir et al., 2009	64%	36%	**p≤0.05**
Bakke et al., 2011	0.9±1.0 OHI	0.3±0.6 OHI	p=0.06
Baram, et al., 2020	1.1±0.6 OH-DSI	N/A	N/A
Barbe et al., 2017 [2]	1.6±0.9	?	N/A
Barbe et al., 2017 [1]	2.0±1.0 PI	1.0 ± 1.0 PI	**p≤0.05**
Fleury et al., 2021	1.3	1.0	**P=0.22**
John et al., 2021	3.1±0.8 OHI	1.3±0.4 OHI	**p≤0.05**
Ledwon et al., 2020	82.9%±20.0 aproximal PI	N/A	N/A
Lyra et al., 2020	37.0±29.4 PI	N/A	N/A
Müller et al., 2011	20.4±30.6 PI	7.3±7.4 PI	**p≤0.05**
Ribeiro et al., 2016	91.8±16.9 PI	64.10±48.9 PI	p=0.23
Rozas et al., 2021	1.6±0.13 OHI-S before brushing	1.0±0.16 OHI-S before brushing	**p≤0.01**
Van Stiphout et al., 2018	60%	31%	**p≤0.01**

Note | N/A = not applicable; % = percentage; PI=Plaque Index; OHI(-S)=Oral Hygiene Index(-Simplified); OH-DSI=Oral Hygiene-Debris Simplified Index

Table 3. Results of periodontal diseases (viz., presence of bleeding, gingivitis, periodontitis, pocket depth, and tooth mobility) in PD patients compared to controls

Periodontal diseases			
	Presence of bleeding		
Article	**PD**	**Control**	**p-value**
Clifford et al., 1995	11.5% self-reported bleeding gums	N/A	N/A
Fleury et al., 2021	57.9%	51.5%	P=0.73
Ledwon et al., 2020	46.2% ±22.9 BI	N/A	N/A
Lyra et al., 2020	19.3 ± 21.1 BoP	N/A	N/A
Müller et al., 2011	7.0 ± 8.3 papilla BI	2.1 ± 2.7 papilla BI	**p≤0.01**
Nakayama et al., 2004	13% self-reported bleeding gums	12% self-reported bleeding gums	NS
Persson et al., 1992	53.3±14.0 BoP	54.9±2.0 BoP	N/A
Van Stiphout et al., 2018	20% self-reported bleeding gums	18.5% self-reported bleeding gums	p=0.21
	Presence of gingivitis		
Article	**PD**	**Control**	**p-value**
Barbe et al., 2017 [2]	1.8±0.8	?	N/A
Barbe et al., 2017 [1]	1.9±0.8 GI	0.8±1.1 GI	**p≤0.01**
Einarsdóttir et al., 2009	60%	40%	**p≤0.05**
Gopalakrishnan et al., 2021	54%	N/A	N/A
John et al., 2021	1.5 ± 0.4 MGI	0.7±0.2	**p≤0.05**
Kennedy et al., 1994	1.4±0.7 GI	1.4±0.7 GI	NS
	Presence of periodontitis		
Article	**PD**	**Control**	**p-value**
Botelho et al., 2011	54%	N/A	N/A
Barbe et al., 2017 [1]	68%	60%	p=0.5
Chang et al., 2016	44.1%	N/A	N/A
Chen et al., 2018	49%	45%	**p≤0.01**
Frota et al., 2016	31.4%	55%	NS
Gopalakrishnan et al., 2021	76%	N/A	N/A
Lyra et al., 2020	75%	N/A	N/A
	Pocket depth		
Article	**PD**	**Control**	**p-value**
Barbe et al., 2017 [2]	18±62.1 CPITN	20±66.7 CPITN	N/A
Cicciù et al., 2012	75.8% teeth with pockets >5	45.0% teeth with pockets >4	N/A
Einarsdottir et al., 2009	4.2mm mean PPD	3.8mm mean PPD	**p≤0.05**
Fleury et al., 2021	3.0mm	3.0mm	NS
	11.1% of PPD ≥ 4 BOP + sites	6.9% of PPD ≥ 4 BOP + sites	P=0.35
Hanaoka et al., 2009	99% pockets >4mm	44% pockets >4mm	**p≤0.05**

John et al., 2021	2.6±0.7 PPDS	1.6±0.4 PPDS	**p≤0.05**
Ledwon et al., 2020	4.0 ±0.9 mean PPD	N/A	N/A
Lyra et al., 2020	2.1±0.8 mean PPD	N/A	N/A
Müller et al., 2011	19.7±36.3 pockets >4mm	2.2±1.1 pockets >4mm	**p≤0.01**
Persson et al., 1992	11.7±8.0 pockets >4mm	8.0±1.26 pockets >4mm	N/A
Schwarz et al., 2006	2.5±0.1 CPITN	2.1 ± 0.1 CPITN	**p≤0.01**
	Tooth mobility		
Article	**PD**	**Control**	**p-value**
Cicciù et al., 2012	29% teeth with mobility grade 2-3	0% teeth with mobility grade 2-3	N/A
Clifford et al., 1995	8.4%	N/A	N/A
John et al., 2021	59%	16%	**p≤0.05**
Ledwon et al., 2020	98.4% (19.7% mobility grade 3)	N/A	N/A
Lyra et al., 2020	1.0 ±2.0 number of teeth with mobility	N/A	N/A
Müller et al., 2011	16.9±37.6 mobility grade 3	0.05±0.23 mobility grade 3	**p≤0.01**
van Stiphout et al., 2018	18.5% self-reported mobility	3.1% self reported mobility	**p≤0.01**

Note | N/A = not applicable; NS= not significant; % = percentage; BI= bleeding Index; BoP=Bleeding on Probing; GI=Gingivitis Index; PPD= Probing Pocket Depth; CPITN= Community Periodontal Index of Treatment Needs; MGI = Modified Gingival Index; PPDS= Probing Pocket Depth Score

Table 4. Results of the presence of caries in PD patients compared to controls.

Caries			
Article	**PD**	**Control**	**p-value**
Anastassiadou et al., 2002	100%	N/A	N/A
Bakke et al., 2011	27% people with caries	7% people with caries	N/A
Chang et al., 2016	48.1% people with caries	N/A	N/A
Cicciù et al., 2012	57.6% DT	48.6% DT	NS
Einarsdottir et al., 2009	22.9±4.4 DMFT	20.6±5.7 DMFT	**p≤0.01**
	87.2±28.4 DMFS	72.0±32.9 DMFS	**p≤0.01**
Fleury et al., 2021	10%	10%	NS
Frota et al., 2016	22.8%	10%	NS
Fukayo et al., 2003	19.3±1.5 DMFT	25.8±0.3 DMFT	**p≤0.01**
Gopalakrishnan et al., 2021	84%	N/A	**N/A**
Hanaoka et al., 2009	53.5% caries lesions	8.1% caries lesions	**p≤0.01**
Kennedy et al., 1994	21.1±5.0 DMFT	16.4±8.0 DMFT	NS
Müller et al., 2011	2.9±6.6 caries lesions	0.7±2.0 carious lesions	**p≤0.01**
Persson et al., 1992	1.1±0.7 DT	2.3±0.3 DT	**p≤0.05**
	3.4±2.0 DS	7.0±1.1 DS	**p≤0.05**
Ribeiro et al., 2016	24.8±3.8 DMFT	26.9±2.2 DMFT	p=0.1
Van Stiphout et al., 2018	74 DT	12 DT	**p≤0.01**

Note | N/A = not applicable; NS= not significant; % = percentage; DT= decayed teeth; DS=Decayed surfaces; DMFT=Decayed, Missing and Filled Teeth; DMFS=Decayed, Missing and Filled Surfaces

Table 5. Results of dental and prosthetic status (viz., number of (missing) teeth, being edentulous, and wearing (partial) dentures and implants) in PD patients compared to controls.

Dental and prosthetic status			
	Number of (missing) teeth		
Article	**PD**	**Control**	**p-value**
Botelho et al., 2011	4.2±? missing NT	N/A	N/A
Bakke et al., 2011	19.1±10.7 NT	24.3±7.3 NT	p=0.1
Baram, et al., 2020	25.6±4.4 NT	N/A	N/A
Cicciù et al., 2012	13 missing NT (median)	9 missing NT (median)	N/A
Einarsdottir et al., 2009	10.24±9.1 missing NT	6.8±8.8 missing NT	**p≤0.05**
Frota et al., 2016	5.7% root remnants	15% root remnants	NS
Hanaoka et al., 2009	14.0±10.7 NT	17.6±9.7 NT	**p≤0.05**
Ledwon et al., 2020	9 NT (median)	N/A	N/A
Lyra et al., 2020	12±7 missing NT	N/A	N/A
Lyra et al., 2021	9.7±10.4	N/A	N/A
Muller et al., 2011	19.1±10.6 missing NT	19.5±8.7 missing NT	NS
Persson et al., 1992	17.0±3.2 NT	14.5±0.78 NT	NS
Ribeiro et al., 2016	10.0±5.2 NT	8.7±3.8 NT	p=0.6
Van Stiphout et al., 2018	21.2±? NT	22.5±? NT	NS
	24 number of root remnants	5 number of root remnants	**p≤0.05**
	Being edentulous and wearing (partial) dentures		
Article	**PD**	**Control**	**p-value**
Anastassiadou et al., 2002	27% edentulous	N/A	N/A
	65% partially edentulous	N/A	N/A
Bakke et al., 2011	15% edentulous	0% edentulous	N/A
	40% fixed or removable prosthesis	26.7% fixed or removable prosthesis	N/A
Baumann et al. 2020	25.7% removable upper prosthesis	26.2% removable upper prosthesis	N/A
	17.1% removable lower prosthesis	19.0% removable lower prosthesis	N/A
Bonenfant et al., 2016	12% edentulous	N/A	N/A
Clifford and Finnerty, 1995	35% partially edentulous	N/A	N/A
	39% edentulous	N/A	N/A
Clifford et al., 1995	30.1% partially edentulous	N/A	N/A
	34.5% edentulous	N/A	N/A
Frota et al., 2016	42.8% edentulous	45% edentulous	NS
	25.7% complete denture	30% complete denture	NS
	34.2% partial denture	25% partial denture	NS
Hanaoka et al., 2009	20.5% edentulous	8.8% edentulous	NS
Lyra et al., 2021	18.2% edentulous	N/A	N/A

Nakayama et al., 2004	42%	13%	N/A
Persson et al., 1992	30% (partial) edentulous	34% (partial) edentulous	N/A
Ribeiro et al., 2016	41.2% edentulous	70% edentulous	N/A
	58.8% partial dentate	30% partial dentate	p=0.08
Ribeiro et al., 2017 [1]	29.4% edentulous (only partial / full edentulous participants)	47.0% edentulous (only partial / full edentulous participants)	N/A
Van Stiphout et al., 2018	12.2% edentulous	12.2% edentulous	NS
Verhoeff et al., 2022	7.9% (partial) edentulous	N/A	N/A
	Implants		
Article	**PD**	**Control**	**p-value**
Bakke et al., 2011	40% fixed or removable prosthesis	26.7% fixed or removable prosthesis	N/A
Baumann et al. 2020	48.6% fixed upper prosthesis	54.8% fixed upper prosthesis	N/A
	28.6% fixed lower prosthesis	23.8% fixed lower prosthesis	N/A

Note | N/A = not applicable; NS= not significant; % = percentage; NT= number teeth

Table 6. Results of case studies and case series, in PD patients .

Article	Number of cases	Age (gender)	Implant type	Location	Torque	Prosthetic	Follow-up Period	Results
Chu et al., 2004	1	83(f)	4 TiUnite; Nobel Biocare 3.5x7.0mm 4.0x7.0mm	LJ	32Ncm	Overdenture (magnetic keepers)	12 months	one magnetic keeper loose
Heckmann et al., 2000	3	71(m); 75(m); 81(f)	2-4 ITI solid screw bone sink depth; Straumann AG 4.1x12mm	LJ; inter-foraminal region	?	Overden-ture; (non-rigid telescopic copings)	45 months	healthy ap-pearance of peri-im-plant bone and stable denture under 50N with gnathody-namom-eter
Liu et al., 2015	1	76(m)	4 NobelSpeedy Groovy RP; Nobel Biocare; 4.0×11.5mm, 4.0×15.0mm,	LJ; bilater-al lateral incisors, bilateral first pre-molars	45-50Ncm	Overdenture (?)	12 months	mucosal soft tissue good condition and no bone loss.
Packer et al., 2009	9	N=9 54-77 (m)	38 Astra-Tech implants (viz., 34 planned activation)	6 LJ; 1 UJ	?	Overden-ture (?)	?	18% implants failed (minimal osseoin-tegration); 100% successful overden-ture place-ment

Note | M=male; F=Female; ? = unknown; LJ=Lower Jaw; UJ= Upper jaw; Ncm= Newton centimeter;

Table 7. Results of the factors associated with oral health problems in PD patients .

Associated factors with oral health in PD patients			
		Gender	
Article	**Males**	**Females**	**p-value**
John et al., 2021	88.9% frequency daily toothbrushing only once	50% frequency daily toothbrushing only once	NS
	16 males moderate-severe gingivitis	11 females moderate-severe gingivitis	NS
	3.11 ± 0.81 OHI	3.05 ± 0.89 OHI	NS
	2.84 ± 0.78 PPD	2.67 ± 0.69 PPD	NS
Lyra et al., 2020	16.8% edentulism	19.6% edentulism	p=0.72
	24.3% severe tooth loss (<9 teeth present)	23.4% severe tooth loss (<9 teeth present)	p=0.66
Müller et al., 2011	20.15 ± 10.22 missing teeth	17.83 ± 11.11 missing teeth	NS
	4.2±8.4 presence of caries	1.4±3.0 presence of caries	**p≤0.05**
Rozas et al., 2021	Oral biofilm composition not associated with gender		NS
		Longer duration of the disease	
Article	**Variable**		**p-value**
Anastassiadou et al., 2002	Dental status not associated with duration of the disease		p=0.93
Bakke et al., 2011	↓ Number of teeth when duration of the disease increases		p=0.08
Barbe et al., 2016	↑ self-reported difficulties in performing oral hygiene when duration of the disease increases		**p≤0.05**
Hanaoka et al., 2009	Number of teeth not associated with disease duration		NS
John et al., 2021	DMFT <3 years (8.0±65.1) compared to >3 years (7.33±3.73) duration of the disease		NS
	OHI <3 years (2.98±0.82) compared to >3 years (3.2±10.85) duration of the disease		NS
	MGI <3 years (1.47±0.39) compared to >3 years (1.57±0.39) duration of the disease		NS
	PPD <3 years (2.47±0.59) compared to >3 years (2.73±0.76) duration of the disease		NS
Van Stiphout et al., 2018	↑ chewing problems when duration of the disease increases		**p≤0.05**
	↑ number of teeth with restorations when duration of the disease increases		**p≤0.05**
	↑ mobility grade when duration of the disease increases		**p≤0.01**

Disease severity (including motor- and non-motor symptoms)		
Article	**Variable**	**p-value**
Anastassiadou et al., 2002	Dental status not associated with disease severity	p=0.14
Bakke et al., 2011	↑ OHI when disease severity increases	**p≤0.01**
Baram et al., 2020	↓ Number of teeth when disease severity increases	**p≤0.05**
	↑ OHI when disease severity increases	p=0.06
Hanaoka et al., 2009	Number of untreated caries leasions not associated with disease severity	NS
	↑ caries lesions when cognitive function decreases	**p≤0.05**
John et al., 2021	↑ OHI for moderate disease severity compared to mild severity	**p≤0.05**
	↑ MGI for moderate disease severity compared to mild severity	**p≤0.05**
	DMFT mild severity (7.24±4.06) compared to moderate severity (9.43±5.68)	NS
	PPD mild severity (2.54±0.60) compared to moderate severity (2.80±0.94)	NS
Ledwon et al., 2020	Number of teeth, tooth mobility, and bleeding index not associated with disease severity	NS
	↑ PI when disease severity increases	**p≤0.05**
Lyra et al., 2020	↑ BoP with increased hand postural tremor, kinetic tremor, and a more depressive state	**p≤0.05**
	↑ plaque, bleeding, and pocket depth when increased rigidity and kinetic tremor of upper extremities are present	**p≤0.05**
	Missing teeth, bleeding, and pocket depth not associated with progression of the disease	NS
Persson et al., 1992	↑ difficulty oral hygiene when hypokinesia is worse	**p≤0.01**
Pradeep et al., 2015	↑ PPD when disease severity increases	**p≤0.01**
	↑ GI when disease severity increases	**p≤0.01**
	↑ PI when disease severity increases	**p≤0.01**
	↑ BoP when disease severity increases	**p≤0.01**
Van Stiphout et al., 2018	↑ chewing and biting problems when severity of PD increases	**p≤0.05**
	↑ daily support needed by performance oral hygiene, when severity of PD increases	**p≤0.01**
	↑ number of teeth with caries lesions and root remnants, when severity of PD increases	**p≤0.01**
	↑ number of teeth with restorations, when severity of PD increases	**p≤0.01**

Medication use		
Article	**Variable**	**p-value**
Barbe et al., 2017	↑ GI when number of prescribed medication increases	**p≤0.05**
Hanaoka et al., 2009	Remaining teeth not associated with LEDD score	NS
Ledwon et al., 2020	Number of teeth, tooth mobility, and bleeding index not associated with number of medications	NS
	↑ PI when number of prescribed medication increases	p=0.06
Rozas et al., 2021	Oral biofilm composition not associated with non-antiparkinsonian medications taken	NS
	PD patients on levodopa/carbidopa showed similar beta-diversity to the controls	NS
	PD patients on levodopa/carbidopa had significantly different oral microbiota than those not taking these medications	**p≤0.05**

Note | N/A = not applicable; NS= not significant; DMFT = Decayed, Missing and Filled Teeth; OHI= Oral Hygiene Index; MGI=Modified Gingival Index; PPD=Probing Pocket Depth; BoP=Bleeding on Probing; LEDD = Levodopa Equivalent Daily Dosage; PI= Plaque Index; GI= Gingivitis Index

Appendix

Appendix 1| Search strategy

PubMed Session Results (20 Jan 2022)

Search	Query	Items found
#9	**#7 OR #8**	2,860
#8	**#1 AND #4**	256
#7	**#5 OR #6**	2,661
#6	#1 AND #3	1,617
#5	#1 AND #2	1,270
#4	((“Quality of Life”[Mesh] OR “quality of life”[tiab] OR “life qualit*”[tiab] OR “living qualit*”[tiab] OR “quality of living”[tiab] OR “Activities of Daily Living”[Mesh] OR “activities of daily living”[tiab] OR “activity of daily living”[tiab] OR “activities of daily life”[tiab] OR “activity of daily life”[tiab] OR “daily living activit*”[tiab] OR “daily life activit*”[tiab] OR “adl”[tiab] OR “chronic limitation of activity”[tiab] OR “self care*”[tiab] OR “Health Status”[Mesh] OR “health status”[tiab] OR “level of health”[tiab] OR “health level*”[tiab] OR “qol”[tiab] OR “hrql”[tiab] OR “hrqol”[tiab]) AND (oral[tiab])) OR “OHRQoL”[tiab]	29,820
#3	“Dyskinesias”[Mesh:NoExp] OR “Mastication”[Mesh] OR “Facial Pain”[Mesh] OR “Facial Neuralgia”[Mesh] OR “Musculoskeletal Pain”[Mesh:NoExp] OR “Myalgia”[Mesh] OR “Arthralgia”[Mesh:NoExp] OR “Neuralgia”[Mesh:NoExp] OR “Burning Mouth Syndrome”[Mesh] OR “Craniomandibular Disorders”[Mesh] OR “Bruxism”[Mesh] OR “Dental Occlusion”[Mesh] OR “Malocclusion”[Mesh] OR “Tooth Wear”[Mesh] OR “oral function*”[tiab] OR “oral dyskinesia*”[tiab] OR “orofacial function*”[tiab] OR “orofacial dyskinesia*”[tiab] OR “mastication”[tiab] OR “chewing”[tiab] OR “tooth mobilit*”[tiab] OR “jaw mobilit*”[tiab] OR “mandibular mobilit*”[tiab] OR “tooth movement*”[tiab] OR “jaw movement*”[tiab] OR “mandibular movement*”[tiab] OR “orofacial pain”[tiab] OR “craniofacial pain”[tiab] OR “myofacial pain”[tiab] OR “facial pain”[tiab] OR “neuropathic pain”[tiab] OR “burning mouth”[tiab] OR “craniomandibular disorder*”[tiab] OR “cranio-mandibular disorder*”[tiab] OR “neuralgia”[tiab] OR “trigeminal”[tiab] OR “Tic Douloureux”[tiab] OR “temporomandibular joint dis*”[tiab] OR “temporo-mandibular joint dis*”[tiab] OR “temporomandibular dysfunction*”[tiab] OR “temporo-mandibular dysfunction*”[tiab] OR “temporomandibular disorder*”[tiab] OR “temporo-mandibular disorder*”[tiab] OR “TMJ dis*”[tiab] OR “TMD”[tiab]	192,191
#2	“Oral Health”[Mesh] OR “Mouth Diseases”[Mesh] OR “Tooth Diseases”[Mesh] OR “Periodontal Prosthesis”[Mesh] OR “Periodontal Index”[Mesh] OR “Prosthodontics”[Mesh] OR “oral health”[tiab] OR “oral hygiene”[tiab] OR “dental”[tiab] OR “dentistry”[tiab] OR “mouth”[tiab] OR “tooth”[tiab] OR “teeth”[tiab] OR “jaw”[tiab] OR “jaws”[tiab] OR “periodont*”[tiab] OR “parodont*”[tiab] OR “Pyorrhea Alveolaris”[tiab] OR “periapical”[tiab] OR “gingiva*”[tiab] OR “gingivi*”[tiab] OR ((“gum”[tiab] OR “gums”[tiab]) AND (“inflammat*”[tiab] OR “disease*”[tiab])) OR “caries”[tiab] OR “carious”[tiab] OR “edentulous”[tiab] OR “prosthes*”[tiab] OR “prosthetic*”[tiab] OR “prosthodont*”[tiab]	982,386
#1	“Parkinsonian Disorders”[Mesh] OR “parkinson*”[tiab]	143,272

Embase.com Session Results (20 Jan 2022)

Search	Query	Items found
#10	**#9 NOT ('conference abstract'/it OR 'conference review'/it)**	4,695
#9	**#7 OR #8**	6,093
#8	**#1 AND #4**	692
#7	**#5 OR #6**	5,547
#6	#1 AND #3	2,045
#5	#1 AND #2	4,009
#4	(('quality of life'/exp OR 'quality of life':ab,ti,kw OR 'life qualit*':ab,ti,kw OR 'living qualit*':ab,ti,kw OR 'quality of living':ab,ti,kw OR 'daily life activity'/exp OR 'activities of daily living':ab,ti,kw OR 'activity of daily living':ab,ti,kw OR 'activities of daily life':ab,ti,kw OR 'activity of daily life':ab,ti,kw OR 'daily living activit*':ab,ti,kw OR 'daily life activit*':ab,ti,kw OR 'adl':ab,ti,kw OR 'chronic limitation of activity':ab,ti,kw OR 'self care*':ab,ti,kw OR 'health status'/exp OR 'health status':ab,ti,kw OR 'level of health':ab,ti,kw OR 'health level*':ab,ti,kw OR 'qol':ab,ti,kw OR 'hrql':ab,ti,kw OR 'hrqol':ab,ti,kw) AND (oral:ab,ti,kw)) OR 'oral health related quality of life'/exp OR 'OHRQoL':ab,ti,kw	45,365
#3	'mastication'/exp OR 'face pain'/exp OR 'musculoskeletal pain'/de OR 'myofascial pain'/exp OR 'arthralgia'/exp OR 'neuralgia'/de OR 'burning mouth syndrome'/exp OR 'temporomandibular joint disorder'/exp OR 'bruxism'/exp OR 'tooth occlusion'/exp OR 'malocclusion'/exp OR 'jaw movement'/exp OR 'oral function*':ab,ti,kw OR 'oral dyskinesia*':ab,ti,kw OR 'orofacial function*':ab,ti,kw OR 'orofacial dyskinesia*':ab,ti,kw OR 'mastication':ab,ti,kw OR 'chewing':ab,ti,kw OR 'tooth mobilit*':ab,ti,kw OR 'jaw mobilit*':ab,ti,kw OR 'mandibular mobilit*':ab,ti,kw OR 'tooth movement*':ab,ti,kw OR 'jaw movement*':ab,ti,kw OR 'mandibular movement*':ab,ti,kw OR 'orofacial pain':ab,ti,kw OR 'craniofacial pain':ab,ti,kw OR 'myofacial pain':ab,ti,kw OR 'facial pain':ab,ti,kw OR 'neuropathic pain':ab,ti,kw OR 'burning mouth':ab,ti,kw OR 'craniomandibular disorder*':ab,ti,kw OR 'cranio-mandibular disorder*':ab,ti,kw OR neuralgia:ab,ti,kw OR trigeminal:ab,ti,kw OR 'Tic Douloureux':ab,ti,kw OR 'temporomandibular joint dis*':ab,ti,kw OR 'temporo-mandibular joint dis*':ab,ti,kw OR 'temporomandibular dysfunction*':ab,ti,kw OR 'temporo-mandibular dysfunction*':ab,ti,kw OR 'temporomandibular disorder*':ab,ti,kw OR 'temporo-mandibular disorder*':ab,ti,kw OR 'TMJ dis*':ab,ti,kw OR TMD:ab,ti,kw	282,483
#2	'oral health related quality of life'/exp OR 'oral health status'/exp OR 'mouth disease'/exp OR 'periodontic device'/exp OR 'dental disease assessment'/exp OR 'prosthodontics'/exp OR 'oral health':ab,ti,kw OR 'oral hygiene':ab,ti,kw OR dental:ab,ti,kw OR dentistry:ab,ti,kw OR mouth:ab,ti,kw OR tooth:ab,ti,kw OR teeth:ab,ti,kw OR jaw:ab,ti,kw OR jaws:ab,ti,kw OR periodont*:ab,ti,kw OR parodont*:ab,ti,kw OR 'Pyorrhea Alveolaris':ab,ti,kw OR periapical:ab,ti,kw OR gingiva*:ab,ti,kw OR gingivi*:ab,ti,kw OR ((gum OR gums) NEAR/3 (inflammat* OR disease*)):ab,ti,kw OR caries:ab,ti,kw OR carious:ab,ti,kw OR edentulous:ab,ti,kw OR prosthes*:ab,ti,kw OR prosthetic*:ab,ti,kw OR prosthodont*:ab,ti,kw	1,181,125
#1	'Parkinson disease'/exp OR 'parkinsonism'/exp OR parkinson*:ab,ti,kw	232,537

Web of Science (Core Collection) Session Results (20 Jan 2022)

Search	Query	Items found
#9	**#7 OR #8**	2,263
#8	**#1 AND #4**	345
#7	**#5 OR #6**	1,982
#6	#1 AND #3	1,083
#5	#1 AND #2	1,148
#4	TS=(((“quality of life” OR “life qualit*” OR “living qualit*” OR “quality of living” OR “activities of daily living” OR “activity of daily living” OR “activities of daily life” OR “activity of daily life” OR “daily living activit*” OR “daily life activit*” OR “adl” OR “chronic limitation of activity” OR “self care*” OR “health status” OR “level of health” OR “health level*” OR “qol” OR “hrql” OR “hrqol”) AND (oral)) OR “OHRQoL”)	29,779
#3	TS=(“oral function*” OR “oral dyskinesia*” OR “orofacial function*” OR “orofacial dyskinesia*” OR “mastication” OR “chewing” OR “tooth mobilit*” OR “jaw mobilit*” OR “mandibular mobilit*” OR “tooth movement*” OR “jaw movement*” OR “mandibular movement*” OR “orofacial pain” OR “craniofacial pain” OR “myofacial pain” OR “facial pain” OR “neuropathic pain” OR “burning mouth” OR “craniomandibular disorder*” OR “cranio-mandibular disorder*” OR “neuralgia” OR “trigeminal” OR “Tic Douloureux” OR “temporomandibular joint dis*” OR “temporo-mandibular joint dis*” OR “temporomandibular dysfunction*” OR “temporo-mandibular dysfunction*” OR “temporomandibular disorder*” OR “temporo-mandibular disorder*” OR “TMJ dis*” OR “TMD”)	121,778
#2	TS=(“oral health” OR “oral hygiene” OR “dental” OR “dentistry” OR “mouth” OR “tooth” OR “teeth” OR “jaw” OR “jaws” OR “periodont*” OR “parodont*” OR “Pyorrhea Alveolaris” OR “periapical” OR “gingiva*” OR “gingivi*” OR ((“gum” OR “gums”) NEAR/3 (“inflammat*” OR “disease*”)) OR “caries” OR “carious” OR “edentulous” OR “prosthes*” OR “prosthetic*” OR “prosthodont*”)	653,348
#1	TS=(“parkinson*”)	195,491

Wiley / Cochrane Library Session Results (20 Jan 2022)

Search	Query	Items found
#9	**#7 OR #8**	497
#8	**#1 AND #4**	260

Appendix 2| Quality assessment of all included studies in the current review.

Table 1. The methodological quality assessment cross-sectional studies, using the Appraisal tool for Cross-Sectional Studies (AXIS tool)

Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Anastassiadou et al. 2002	yes	yes	no	yes	yes	?	?	no	no	yes
Bakke et al. 2011	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Barbe et al. 2016	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Barbe et al. 2017	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Barbe et al. 2017	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Baumann et al. 2020	yes	yes	yes	yes	yes	no	?	yes	yes	yes
Bonefant et al. 2016	yes	yes	yes	yes	yes	no	?	yes	yes	yes
Chen et al. 2018	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Clifford et al., 1995	yes	yes	no	yes	yes	no	?	?	?	no
Clifford et al., 1998	yes	yes	no	yes	yes	no	?	yes	?	no
Cicciù et al. 2012	yes	yes	yes	yes	yes	no	?	yes	yes	no
Einarsdóttir et al. 2009	yes	yes	no	yes	yes	yes	?	yes	yes	no
Fleury et al. 2021	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Frota et al. 2016	yes	yes	no	yes	yes	yes	?	yes	yes	yes
Fukayo et al. 2003	yes	yes	yes	yes	yes	no	?	yes	yes	yes
Gopalakrishnan et al. 2021	yes	yes	no	no	?	?	?	no	no	no
Hanaoka et al., 2009	yes	yes	yes	yes	yes	no	?	yes	yes	yes
John et al. 2021	yes	yes	yes	yes	yes	?	?	yes	yes	yes
Kennedy et al. 1994	yes	yes	yes	yes	yes	?	?	yes	yes	yes
Lyra et al. 2020	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Martinez-Martin et al. 2017	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Mattos et al. 2019	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Müller et al. 2011	yes	yes	yes	yes	yes	no	?	yes	yes	yes
Nakayama et al., 2004	yes	yes	yes	yes	yes	no	?	yes	yes	yes
O'Neill et al. 2021	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Packer et al. 2009	yes	yes	no	yes	yes	yes	?	yes	yes	no
Persson et al. 1992	yes	yes	no	yes	yes	yes	?	yes	yes	yes
Pradeep et al. 2015	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Ribeiro et al. 2016	yes	yes	yes	yes	yes	?	?	yes	yes	yes
Ribeiro et al. 2017	yes	yes	yes	yes	yes	no	?	yes	yes	yes
Ribeiro et al. 2017	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Rozas et al. 2021	yes	yes	yes	yes	yes	yes	?	Yes	yes	yes
Schwarz et al. 2006	yes	yes	yes	yes	yes	no	?	yes	yes	no
van Stiphout et al. 2018	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
Verhoeff et al. 2022	yes	yes	yes	yes	yes	no	yes	yes	yes	yes

Note|[1]= item is reverse scored; ?= unclear; Q=question; Q1=where the aims/objectives of the study clear? Q2=was the study design appropriate for the stated aim(s); Q3=was the sample size justified?; Q4=was the target/reference population clearly defined? (is it clear who the research was about?); Q5=was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?; Q6=was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?; Q7=were measures undertaken to address and categorise non-responders?; Q8=were the risk factor and outcome variables measured appropriate to the aims of the study?; Q9=were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled,

Q11	Q12	Q13[1]	Q14	Q15	Q16	Q17	Q18	Q19[1]	Q20	AXIS score/20
no	no	no	N/A	no	yes	no	yes	yes	yes	9
yes	yes	no	N/A	yes	yes	yes	yes	?	yes	17
yes	yes	no	N/A	yes	yes	yes	yes	?	yes	17
yes	yes	no	N/A	yes	yes	yes	yes	?	yes	17
yes	yes	no	N/A	yes	yes	yes	yes	?	yes	17
yes	yes	no	N/A	yes	yes	yes	yes	?	yes	16
yes	yes	no	N/A	yes	yes	yes	yes	?	yes	16
yes	yes	no	N/A	yes	yes	yes	yes	no	yes	18
no	no	no	N/A	yes	yes	yes	yes	?	no	9
no	no	no	N/A	yes	no	yes	no	?	yes	9
no	yes	no	N/A	yes	yes	yes	yes	no	yes	14
no	no	no	N/A	yes	no	yes	no	?	yes	11
yes	yes	yes	N/A	yes	yes	yes	no	no	yes	17
yes	yes	yes	N/A	yes	yes	yes	no	?	yes	15
yes	no	no	N/A	yes	yes	yes	yes	?	?	13
no	no	no	N/A	yes	no	yes	no	no	yes	6
yes	yes	no	N/A	yes	yes	yes	no	?	yes	15
yes	yes	no	N/A	yes	yes	yes	yes	no	yes	17
yes	yes	no	N/A	?	yes	yes	no	?	yes	14
yes	yes	no	N/A	yes	yes	yes	yes	no	yes	17
yes	yes	no	N/A	?	yes	yes	yes	no	yes	16
yes	yes	no	N/A	yes	yes	yes	yes	no	yes	17
yes	yes	no	N/A	?	yes	yes	yes	?	yes	15
yes	yes	no	N/A	yes	yes	yes	yes	?	yes	15
yes	yes	no	N/A	yes	yes	yes	yes	?	yes	17
no	yes	no	yes	yes	yes	yes	yes	?	yes	15
no	yes	no	N/A	yes	yes	yes	yes	no	no	14
yes	yes	no	N/A	?	yes	yes	no	no	yes	15
yes	yes	no	N/A	yes	yes	yes	?	?	yes	15
yes	yes	no	N/A	yes	yes	yes	yes	?	yes	16
yes	no	no	N/A	?	yes	yes	yes	?	yes	15
yes	yes	no	N/A	yes	yes	yes	yes	no	yes	17
no	no	?	N/A	?	no	yes	yes	?	?	10
yes	yes	no	N/A	yes	yes	yes	yes	no	yes	18
yes	yes	yes	yes	yes	yes	yes	yes	no	yes	18

piloted or published previously?; Q10=is it clear what was used to determine statistical significance and/or precision estimates? (e.g. p-values, confidence intervals); Q11=were the methods (including statistical methods) sufficiently described to enable them to be repeated?; Q12=were the basic data adequately described?; Q13=does the response rate raises concerns about non-responders bias?; Q14=if appropriate, was information about non-responders described?; Q15=were the results internally consistent?; Q16=were the results presented for all the analyses described in the methods?; Q17=were the author's discussions and conclusions justified by the results?; Q18=were the limitations of the study discussed?; Q19=were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?; Q20=was ethical approval or consent of participants attained?; N/A= not applicable

Table 2. The methodological quality assessment RCT studies, using the Cochrane Risk of Bias Tool

Paper	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Baram et al., 2020	-	+	+	-	-	+

Note| RCT=Randomized Controlled Trial; + = bias is present ; - =bias is not present

Table 3. The methodological quality assessment cohort studies, with Newcastle-Ottawa Quality Assessment form for Cohort studies (NOS)

	Selection	Selection	Selection	Selection	Comparability	Outcome	Outcome	Outcome	Quality
Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	
Botelho et al., 2020	b(1)	a(1)	a(1)	b(1)	c	b(1)	b(1)	d	poor quality
Chang et al., 2016	a(1)	a(1)	a(1)	a(1)	b(1)	b(1)	a(1)	d	good quality
Ledwon et al., 2020	a(1)	a(1)	a(1)	a(1)	b(1)	b(1)	b	d	poor quality

Note | NOS = Newcastle-Ottawa Scale, ( ) = number of stars; Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in the outcome.

Table 4. The methodological quality assessment case-reports, using the JBI critical appraisal checklist for Case Reports

Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total
Chu et al., 2004	yes	no	no	no	yes	no	no	yes	3
Heckman et al., 2000	yes	yes	yes	no	yes	yes	yes	yes	7
Liu et al., 2015	yes	no	yes	yes	yes	yes	no	yes	6
Packer et al., 2015	no	no	yes	no	no	no	no	yes	2

Note| Q1= Were the patient's demographic characteristics clearly described?; Q2= Was the patient's history clearly described and presented as a timeline?; Q3= Was the current clinical condition of the patient on presentation clearly described?; Q4= Were diagnostic tests or assessment methods and the results clearly described?; Q5= Was the intervention(s) or treatment procedure(s) clearly described?; Q6= Was the post-intervention clinical condition clearly described?; Q7= Were adverse events (harms) or unanticipated events identified and described?; Q8= Does the case report provide takeaway lessons?

Chapter 3

Salivation in Parkinson's disease: a scoping review

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Abstract

Background: in patients with Parkinson's disease, there may be complaints of salivary problems such as xerostomia or drooling. This can have consequences for their oral health and quality of life. To date, systematic reviews have focused on drooling only.

Objectives: we aimed to provide an overview of the available literature that includes both objective assessments (namely, hypersalivation and hyposalivation) and the subjective experience (namely, xerostomia and drooling) of salivary problems in patients with Parkinson's disease .

Methods: a literature search in 4 databases was performed up to February 12, 2021. Two researchers independently assessed studies for eligibility.

Results: in total, 63 studies were included. The prevalence of self-reported xerostomia ranged from 49% to 77%, and that of self-reported drooling from 5% to 80%. Ten articles reported a significantly lower mean salivary flow in Parkinson's disease patients than in controls. None of the articles with both a control group and a patient group reported a significantly higher salivary flow in patients with Parkinson's disease. When questioned about subjective salivary problems, a significantly higher prevalence of both xerostomia (7 studies) and drooling (14 studies) was found in patients with Parkinson's disease than in controls. Patients with Parkinson's disease have a lower salivary flow rate and higher prevalence of both xerostomia and drooling than controls.

Conclusion: the complexity of salivary problems present in Parkinson's disease patients necessitates a multidisciplinary approach in order to avoid mutually counteracting treatments from different healthcare professionals.

Keywords: xerostomia, dental health, elderly, review, saliva

Introduction

Parkinson's Disease is a neurodegenerative condition commonly affecting older people[1]. Parkinson's Disease has a complex phenotype presenting with a wide range of symptoms. Both motor symptoms (e.g., bradykinesia, freezing of gait and tremor) and non-motor symptoms (e.g., loss of smell and depression) can occur[1]. The number of people with Parkinson's Disease has been estimated to be 2-3 per 1000 persons in the Netherlands. As older people are more affected by Parkinson's Disease, the number of persons affected is expected to increase, due to ageing[2]. Worldwide, the number of people affected by Parkinson's Disease is approximately 6.1 million people[3].

Patients with Parkinson's Disease use many different types of medication to suppress either motor and non-motor symptoms, or symptoms arising from comorbid conditions. Affected patients may receive many and varied medication per day and polypharmacy, defined as five or more actively prescribed drugs, is commonly present in those with Parkinson's Disease[4]. McLean et al. reported a prevalence of polypharmacy in patients with Parkinson's Disease, living in Scotland, of 64%[5]. A well-known consequence of polypharmacy is hyposalivation (i.e., objectively lower salivary flow) or xerostomia (i.e., the subjective feeling of a dry mouth)[6–8]. Additionally, the pharmacodynamics of anti-parkinsonian medications (e.g., both xerogenic and stimulatory effects) may also play a role in salivary flow. Separate to xerostomia, drooling is also reported by patients affected by Parkinson's Disease. It is important to recognise that, while hypersalivation may result in drooling, the terms are not synonymous. The former is an objective increase in salivation, whereas drooling is the loss of saliva externally from the confines of the oral cavity. In Parkinson's Disease,[9] a lack of control over the masticatory muscles is one factor implicated in drooling[10,11]. [12].

Salivary problems can lead to both physical and psychological problems. For example, speaking and eating may become increasingly difficult; the latter could result in gastrointestinal symptoms, like digestive complaints[13]. Moreover, difficulties with lubrication of the oral environment can result in, for example, failing protection of the dental hard tissues, with worsened oral health status and resultant social impairment[14,15]. Xerostomia and drooling can also affect oral health-related quality of life (OHRQoL)[15–17].

Concerning salivary problems in Parkinson's Disease, only systematic reviews on drooling have been published so far[18,19]; none have specifically evaluated hyposalivation and xerostomia. However, insight into the varying salivary problems in patients with Parkinson's Disease is important. Although it seems paradoxical, it is possible that drooling and hyposalivation may present in the same patient, while patients and caregivers in daily practice mostly complain about drooling. Furthermore, it is possible that different professional groups are focused on either hypersalivation or hyposalivation in their treatment, depending on their specific professional backgrounds.

In this scoping review, we aimed to provide an overview of both the measured salivary flow and the presence of subjectively experienced salivary problems in Parkinson's Disease patients. We also aimed to discuss the aetiological pathways for all types of salivation problems possible in patients with Parkinson's Disease.

Material & Methods

Search

A literature search was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement (www.prisma-statement.org)[20]. To identify all relevant publications, we conducted systematic searches in the bibliographic databases PubMed, Embase.com, Wiley/Cochrane Library, and Web of Science from inception up to February 12, 2021 in collaboration with a medical librarian (RdV).

The following terms were used (including synonyms and closely related words) as index terms or free-text words: "Sialorrhea", "Xerostomia", "Saliva", and "Parkinson disease". The reference lists of the identified articles were searched for relevant publications. Duplicate articles were excluded. The full search strategies for all databases can be found in Appendix 1.

Inclusion and exclusion criteria

Titles, abstracts, and full texts were screened according to the following inclusion criteria: (1) Parkinson's Disease patients; (2) cohort studies, cross-sectional studies, case-control studies, case-reports, qualitative studies, randomized controlled trials; and (3) articles in English or Dutch. The exclusion criteria were: (1) patients with other movement disorders than Parkinson's Disease; (2) full text cannot be retrieved or no full text is available; (3) results are presented as abstracts and not as full-text articles; and (4) other languages than English or Dutch.

Study selection

Two reviewers (MV and MK) independently screened all potentially relevant titles and abstracts for eligibility. If necessary, the full text article was checked for the eligibility criteria. Differences in judgement were resolved through a consensus procedure. The full text of the selected articles was obtained for further review. The reference lists of the identified articles were screened for relevant studies which were not found in the search.

Quality assessment

One reviewer (MV) evaluated the methodological quality of the full text papers, using the methodological quality assessment for cross-sectional studies, with the Appraisal tool for Cross-Sectional Studies (AXIS tool)[21]. This tool assesses cross-sectional studies on relevance and reliability, focussing on aspects like selection bias, response bias, and internal consistency. The maximum quality score is 20. When cohort studies were included, only the cross-sectional part of the studies was used (N=3). Thus, the AXIS tool could be used to assess the quality of those studies as well.

Data extraction

One reviewer (MV) extracted the data from the included articles, which was checked by the second reviewer (MK). The following data was extracted from the articles: (1) characteristics of the study (e.g., country, study design, sample size, available control group); (2) characteristics of the

participants (e.g., age, gender, disease duration and severity, medication used, LEDD (i.e., levodopa equivalent daily dosage)); and (3) outcome measures (e.g., salivation problems as described earlier and unstimulated or stimulated salivary flow), measurement tools, prevalence, and salivary flow in ml/min). A distinction was made between studies using objective and subjective outcome measures (Table 1 and 2, respectively).

Analysis

All studies were analysed using descriptive data, mostly as percentages and means, including the standard deviation. The varied questionnaires and study designs meant that the included studies were not methodologically homogeneous enough to allow a meta-analysis.

Results

Study selection and characteristics

The literature search generated 3664 references: 659 in PubMed, 1985 in Embase, 268 in Cochrane, and 734 in Web of Science. After removing duplicates of references that were selected from more than one database, 2435 references remained. The flow chart of the search and selection process is presented in Appendix 2. Following the study-selection procedure, a total of 63 studies were included: 3 cohort studies and 60 cross-sectional studies. Characteristics of the included studies are described in Tables 1 and 2. The included studies originated from 28 different countries. For a better overview, a distinction was made between studies using objective and subjective outcome measures. In total, 534 participants with Parkinson's Disease were involved in the objective studies, and 11670 participants were included in the subjective studies. The objective and subjective study participants had a mean age of 67 ± 7 and 62 ± 17 years, respectively (Tables 1 and 2). Only two of the included articles reported both objective data and subjective data[22,23]. As can be seen in Table 2, there is a large number of differences in measurements assessing objective salivary flow (N=6) and subjective salivary problems (namely, xerostomia (N=3) and drooling (N=8)). The majority of the studies that analysed xerostomia (N=11) and drooling (N=12) used various (unpublished) self-administered questionnaires.

Quality assessment

The assessment of the quality of the included articles is summarized in Appendix 3. The AXIS scores ranged from 8 to 19. All studies suffered from the difficulty of including sufficient numbers of participants with Parkinson's Disease. Most had therefore recruited study participants from local societies of Parkinson's Disease patients. This could have resulted in some bias, thus yielding lower AXIS scores. In 93% (N=13) of the objective studies and 83% (N=43) of the subjective studies, the required sample size was not calculated, described, or justified. Furthermore, in 33% (N=21) of the studies, not all characteristics of the study sample were clearly described.

Studies with objective measurements

In total, 8 articles analysed the difference in unstimulated salivary flow between Parkinson's Disease patients and a control group (Table 1). Of these, 7 articles showed a significantly lower salivary flow in the patient group than in the control group[24–30]. One study did not show a significant difference between both groups[31] (Figure 1). Furthermore, there were 7 studies that analysed the stimulated salivary flow (Table 1)[22,23,25,30,32–34]. Two studies used acid to stimulate the salivary flow[25,30] and 5 studies used stimulation by means of chewing[22,23,32–34]. In 3 articles, a significant difference was found, whereby the patient group showed a lower salivary flow than in the control group (Figure 2)[22,23,25]. However, 4 articles did not show a significant difference in salivary flow rate between patients and controls[30,32–34]. In summary, none of the articles showed a significantly greater salivary flow rate in Parkinson's Disease patients than in controls.

In 3 objective studies, the correlation between severity of the disease with salivary flow was analyzed [26,27,33]. Huskic, et al. found no correlation between these two factors[27]. However, Fedorova, et al. found a weak positive correlation (r=0.3)[26], and Persson et al. found that when the degree of hypokinesia was higher, a lower salivary flow was present[33]. There were two objective studies that analysed whether there was a correlation between the duration of the illness and the salivary flow, but none could be established[26,30].

On the association between the use of dopaminergic medication and salivary flow, Bagheri found no significant difference in salivary flow rate between treated patients with Parkinson's Disease and *de novo* (namely, non-treated) patients[24]. Also, Huskic and Tumilasci did not find a correlation between medication usage of anti-parkinsonian medication and dosage of levodopa and salivary flow[27,30]. However, Barbe found a moderate negative correlation between the number of medications and salivary flow (r=-0.4) as well as between medication dosages and salivary flow (r=-0.4)[22].

Studies with subjective measurements

In total, 12 articles described the reported frequencies of xerostomia (Table 2). The presence of xerostomia ranged from 49% to 77%. Of the 7 articles where a control group was involved, the presence of xerostomia ranged from 50% to 65% in the patient groups, and from 0% to 32% in the control groups[22,23,35–39]. In all 7 articles, a statistically significant higher presence of xerostomia was found between individuals with Parkinson's Disease and the control group, whereby xerostomia was more common in the former than in the latter (Figure 3)[22,23,35–39].

48 articles analysed the self-reported frequencies of drooling in patients with Parkinson's Disease (Table 2). The frequency of drooling ranged from 5% to 80% (Figure 4). In 18 articles, a control group was included, although three of these did not investigate whether there was a difference between the groups. [40–42]. However, 15 articles did analyse the difference between the control and patient groups, and 14 of these showed a significant difference[1,35,36,43–53]. The presence of drooling in the control group ranged from 0% to 17%. Only one article did not show a significant difference between the two groups[38].

Discussion

The aim of this scoping review was to provide a systematic and critical overview of the literature on salivary flow rate and subjectively experienced xerostomia and drooling in patients with Parkinson's Disease. Furthermore, we aimed to discuss the potential aetiological pathways for all types of salivation problems. In total, 63 studies were included. The presence of xerostomia in patients with Parkinson's Disease ranged from 49% to 77%, and that of drooling from 5% to 80%. When patients with Parkinson's Disease reported their own experience concerning salivary problems, either xerostomia (7 studies) or drooling (14 studies) were found to be more common than in controls. In 7 articles, a lower unstimulated salivary flow was found, and in 3 articles, a lower stimulated salivary flow was observed in Parkinson's Disease patients than in a control group. None of the articles with both a control group and a patient group reported a higher salivary flow in patients with Parkinson's Disease. Although some of these findings appear contradictory, the mechanisms involved in xerostomia and drooling complaints are likely not the same. Also, there is a lack of studies combining both objective measurements and subjective complaints. Therefore, it is currently not possible to determine to what extent these phenomena are present in the same individual.

Hypersalivation and drooling

Some authors have suggested that motor symptoms of Parkinson's Disease (e.g., posture, hypomimia, reduced spontaneous swallowing) are important aetiologic factors for drooling[18,39,54,55]. The stooped posture and loss of facial motor skills promote anterior saliva loss, aided by gravity. Interestingly, hypersalivation is seldom mentioned as a possible aetiology for drooling and in this scoping review no higher salivary flow rate was found. Nevertheless, treatment options to manage drooling are primarily based on decreasing the amount of saliva. In the literature, two explanations for potential hypersalivation in patients with Parkinson's Disease were noted. First, poor oral health (e.g., carious lesions, periodontal inflammation) is mentioned as a risk factor for increased salivation. In earlier research, the poorer oral health of patients with Parkinson's Disease than in a healthy control group was described[39]. Second, some medication types are described as a possible aetiology of hypersalivation. Individual drugs like levodopa and clozapine, used to supplement dopamine and relieve psychotic symptoms, respectively, in Parkinson's Disease, are known to be associated with hypersalivation. Hypersalivation may be encountered in 30-80% of patients treated with clozapine[56]. Since dopamine modulates saliva secretion, treatment with levodopa can also modulate salivation. However, the available studies do not appear to strongly support this notion. Ou et al. looked at the association between levodopa and hypersalivation and found that when data were corrected for age, disease duration, and disease severity, the association between levodopa and hypersalivation found in the univariate analysis, was no longer observed. In two other studies, no association between levodopa usage and hypersalivation was found[24,33]. Only Proulx et al. showed that when corrected for age, sex, and severity of Parkinson's Disease, the production of saliva was negatively correlated with levodopa usage. The latter study was not included in this scoping review, because the used volume of salivary flow rate was probably miscalculated (i.e., the flow rate is described as mg/min; recalculation in ml/min yielded unrealistically small numbers equal to zero for both controls and PD

patients). In summary, the studies included in this review showed that levodopa use is probably not associated with higher salivary flow rate.

Two possible explanations for why drooling can occur in Parkinson's Disease have been identified. First, a study using scintigraphy showed that no greater secretion of saliva was apparent in patients with Parkinson's Disease. Instead, the excretion level (i.e., the time to release saliva from the gland) was higher[19]. When combining the latter with, amongst others, a poorer muscle control, drooling could appear. Second, when focusing on pathophysiologic causes for drooling, Hou et al. used fMRI to examine brain structures in drug-naive Parkinson's Disease patients who were either droolers or non-droolers. In the group that experienced saliva loss, the functional connectivity of brain structures, such as the putamen and right occipital and temporal lobes, was found to be lower than in non-droolers. In conclusion, changes in interactions between brain regions could contribute to the aetiology of drooling in Parkinson's Disease.

Hyposalivation and xerostomia

Although in the above paragraphs we report that drooling occurs in many patients with Parkinson's Disease, the observational studies in the current review showed that hyposalivation predominates (Figures 1 and 2)[22,31]. Although only two studies showed salivary flow rates for PD patients below the cut-off criteria for hyposalivation (<0.1mL/min for unstimulated saliva and <0.7mL/min for stimulated saliva), the majority of the studies (N=9) showed significantly lower flow rates for Parkinson's Disease patients than in their peers. The varied salivary collection methodologies in the included studies (e.g., draining, spitting, suction) and the difference in the number of salivary glands involved (viz., individual salivary gland or mixed salivary glands) prevents us from analysing these cut-off criteria across studies To date, most studies have focussed on the presence and/or severity of hyposalivation; few have examined the pathophysiology. Normally, cholinergic stimulation results in a higher amount of (and more aqueous) saliva. However, in patients with Parkinson's Disease, a higher level of activity of the enzyme acetylcholinesterase (AChE) has been found in saliva than in controls[26]. Increased salivary AChE has been proposed to be a potential marker[26,57] for the poorer cholinergic function in patients with Alzheimer's disease[26]. This could result in lower salivary flow. Also, Lewy body pathology[26,37] was found in the parasympathetic nervous system, including in the submandibular ganglion, and a-synuclein pathology[26] was found in the submandibular gland in nearly all Parkinson's Disease patients, and this may also negatively affect salivary flow. Hence, the presence of pathology was suggested with the possible consequence of hyposalivation[26]. Furthermore, anticholinergic medications such as tricyclic antidepressants, are often used by Parkinson's Disease patients, and are known for their antimuscarinic effect on the parasympathetic system. As previously mentioned, the polypharmacy is also considered to be a risk factor for hyposalivation and/or xerostomia In the majority of Parkinson's Disease patients (93%), comorbidities (e.g., dementia, depression) were present. These comorbidities have the consequence that complex medicinal regimes are needed to suppress not only the symptoms caused by Parkinson's Disease but also the comorbidities and side-effects of the drugs. Barbe et al. showed that there is a correlation between unstimulated salivary flow and the number of medication types or the LEDD score[22]. All this is in accordance with

our finding that objectively assessed hyposalivation is more likely to be present in patients with Parkinson's Disease than in controls.

Clinical consequences

Saliva has a broad beneficial function for oral health and the gastrointestinal tract. Saliva ensures lubrication of the oral mucosa and dental hard tissues. It also facilitates oropharyngeal and oesophageal cleansing. Saliva also helps with the digestion of food and with taste perception. When hyposalivation is present, people can have a higher risk of candida infection, carious lesions, tooth wear (namely, mechanical or chemical), or swallowing difficulties[58,59]. When oral health is worsened or it is harder to eat due to the above difficulties, food intake decreases. As a consequence, weight loss and less stimulation of the salivary flow due to less mastication may occur. It has been suggested that impaired mastication and tooth loss are associated with declines in cognitive function[60]. Drooling can also be complicated by angular cheilitis. This, along with the act of drooling itself, can lead to social embarrassment and resultant social isolation. Due to both objective and subjective salivary problems, the OHRQoL could deteriorate. In conclusion, an increased or decreased salivary flow rate can lead to physical as well as psychosocial problems[59].

Limitations of the study and suggestions for future research

Although this is the first scoping review including all types of salivary problems in patients with Parkinson's Disease, some limitations have to be pointed out. First, more studies with a questionnaire-based design than objective clinical studies (N=13), were included in this review (N=52). To date, only two studies have examined both subjectively experienced salivary problems and objectively measured salivary flow rate. Thus, it is not possible to determine how often hyposalivation and drooling co-occur. In future studies, this combination is recommended to be examined, because treatment of drooling based on reducing salivary flow should be reconsidered when hyposalivation is, or might be, present. Second, different terms are used in the included articles. Some articles use the term 'drooling' if hypersalivation occurs. Also, confusingly, studies used different terms, like "dribbling of saliva" and "sialorrhea". "Dribbling of saliva" could give the impression that it is less severe than "sialorrhea", so there is a risk for interpretation bias included in the question used. Third, a limitation of this study is the number of different questionnaires (N=10) used to examine self-reported salivary problems. Thus, it is not possible to combine the data found in this study and perform a meta-analysis. Fourth, drooling (N=40) was examined to a greater extent than xerostomia problems (N=4) or both (N=8) in self-report studies (Tables 1 and 2). Fifth, the majority of included articles did not have a main focus on salivary problems in patients with Parkinson's Disease. Most of the time, salivary problems were part of the non-motor symptoms that were analysed. Sixth, the difficulty of polypharmacy and correcting for individual medication types that influence salivation problems is complicated in this patient group. In summary, the results of this scoping review point to a compelling need to examine objectively measured hypo- and hypersalivation in combination with assessment of subjective xerostomia and drooling in a population with Parkinson's Disease, where the severity of the disease and medication usage are systematically analysed.

Clinical importance

For dentists, it is important to be aware that a pathologically dry mouth is more prevalent in Parkinson's Disease patients than in controls, with consequences for the oral environment. However, drooling can also occur, with psychosocial consequences. Since poor oral health affects, amongst others, quality of life, multidisciplinary management of salivary problems in patients with Parkinson's Disease is needed.

Conclusion

The included articles showed a lower salivary flow rate in patients with Parkinson's Disease than in the control group. Subjectively, patients with Parkinson's Disease reported a significantly higher prevalence of xerostomia or drooling, than in controls. A multidisciplinary approach for salivary problems in patients with PD is urgently needed, so as to avoid mutually counteracting treatments from different healthcare professionals[61].

Data availability: the data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest statement: the authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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Figures and tables

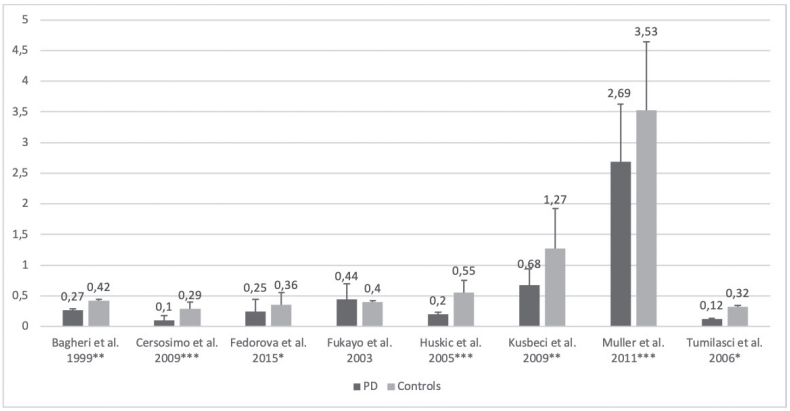


Figure 1. Unstimulated salivary flow rate (ml/min) for patients with Parkinson's disease (dark grey) vs. Controls (light grey), with the corresponding standard deviations.
Note|*= p<0.05; **= p<0.01; ***= p£0.001;

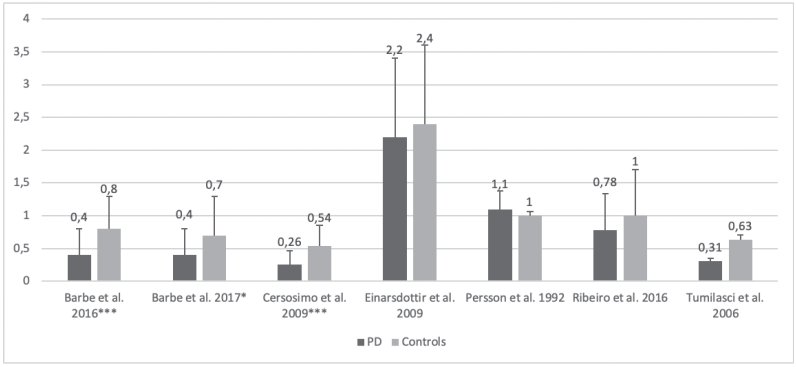


Figure 2. Stimulated salivary flow rate (ml/min) for patients with Parkinson's disease (dark grey) vs. controls (light grey), with the corresponding standard deviations.
Note|*= p<0.05; ***= p£0.001;

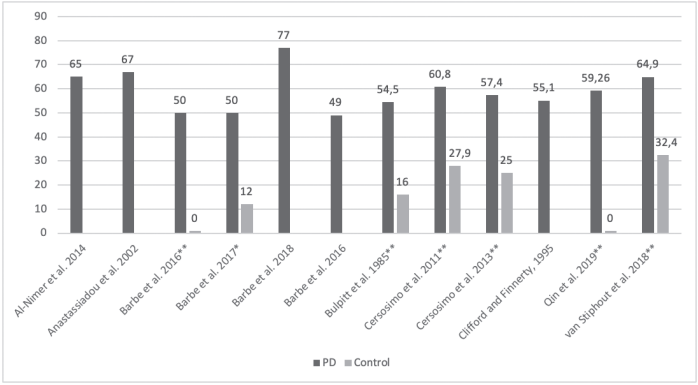


Figure 3. Prevalence (%) of xerostomia for patients with Parkinson's disease (dark grey) vs. controls, when applicable (light grey). Note|*= p<0.05; **= p≤0.001

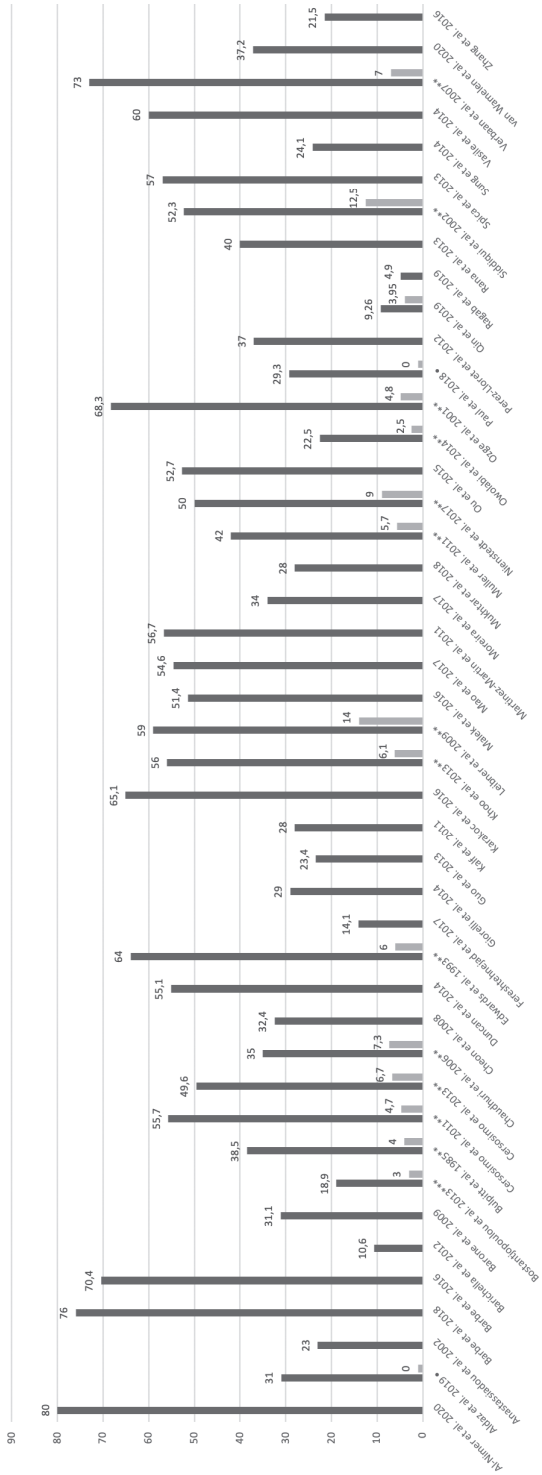


Figure 4. Prevalence(%) of drooling for patients with Parkinson's disease (dark grey) vs. controls, when applicable (light grey). Note I*= p<0.05; **= p≤0.001; •=not analysed

Table 1. Characteristics of the included studies, in which an objective assessment of salivary problems (namely, hyposalivation and/or hypersalivation) was performed

Study	Country	Design	Np [N]	Nc [N]	Age PD [M±SD]	Male gender PD [N(%)]
Bagheri et al. 1999	France	CS	83	65	66.8 ± 1.0	47 (57%)
Barbe et al. 2016	Germany	CS	30	30	69.3 ± 8.0	17 (57%)
Barbe et al. 2017	Germany	CS	26	26	69.0 ± 9.0	14 (54%)
Cersosimo et al. 2009	Argentina	CS	20	11	67 ± 11	8 (40%)
Einarsdottir et al. 2009	Iceland	CS	67	55	?	39 (58%)
Fedorova et al. 2015	Denmark	CS	30	49	63.7 ± 9.1	16 (53%)
Fukayo et al. 2003	Japan	CS	31	104	?	17 (49%)
Huskic et al. 2005	Sarajevo	CS	16	16	?	8 (50%)
Kusbeci et al. 2009	Turkey	CS	37	30	66.1 ± 8.2	20 (54%)
Muller et al. 2011	Germany	CS	101	75	66.2 ± 10.5	55 (54%)
Persson et al. 1992	Sweden	CS	30	585	73 ± 7.3	17 (57%)
Ribeiro et al. 2016	Brazil	CS	17	20	69.41 ± 4.65	9 (53%)
Tumilasci et al. 2006	Argentina	CS	46	13	61.6 ± 2.4	17 (74%)

Note| CS=cross sectional; Np = number of Parkinson's Disease patients; Nc= number of controls; N= numbers; M=mean; SD =standard deviation; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; HY=Hoehn & Yahr rating scale; APM = antiparkinsonian medication; LEDD= Levodopa Equivalent Daily Dosage; U=Unstimulated; Sc=Stimulated chewing; Ss=Stimulated sour; Uss=Unstimulated and Stimulated sour; ?=unknown; #= 12h no medication; * =part II MDS-UPDRS; [a] = during OFF status

Duration disease [M±SD]	Disease severity MDS-UPDRS (part III)	Disease severity HY scale	APM [Y/N]	LEDD (mg/day±SD)	Salivation type [U/S/US]	Measurement tool
?	?	2.82 ± 0.50	Y	?	U	Cotton roll
8.0 ± 4.3	12.0 ± 8.8*	?	Y	661.2 ± 376.7	Sc	Cup; Paraffin
9.0 ± 4.0	13.0 ± 9.0*	?	Y	680 ± 385	Sc	Cup; Paraffine
0.67 ± 0.25	13.8 ± 5.7	1.7 ± 0.44	N		USs	Vacuum; Citric
?	?	?	?	?	Sc	Cup; gum
4.8 ± 3.3	27.0 ± 12.8	1.9 ± 0.5	Y#	?	U	Cup
?	?	?	Y	?	U	(paper) Cup
?	?	?	Y	?	U	Tubes
?	?	2.35 ± 0.50	Y	474.6 ± 165	U	Tube
?	30.64 ± 13.78	2.72 ± 0.84	?	?	U	?
11 ± 5.4	?	?	Y	?	Sc	Paraffin
6.76 ± 3.80	?	?	Y	?	Sc	Parafilm
8.7	32.7[a]/14.7	?	Y	?	Uss	Vacuum; citric

Table 2. Characteristics of the included studies, in which a subjective assessment of salivary problems (namely, drooling and/or xerostomia) was performed

Study	Country	Design	Np [N]	Nc [N]	Age PD [M±SD]	Male gender PD [N(%)]
Al-Nimer et al. 2014	Iraq	CS	20	20	64.4 ± 10.6	16 (80%)
Aldaz et al. 2019	Spain	CS	45	25	66.13 ± 9.95	23 (51%)
Anastassiadou et al. 2002	Greece	CS	51	na	67.5 ± 2.8	32 (63%)
Barbe et al. 2016	Germany	CS	30	30	69.3 ± 8.0	17(57%)
Barbe et al. 2017	Germany	CS	26	26	69.0 ± 9.0	14(54%)
Barbe et al. 2018	Germany	CS	75	na	69.0 ± 8.0	43 (57%)
Barbe et al. 2016	Germany	CS	100	na	71 ± 8.7	72 (72%)
Barichella et al. 2012	Italy	CS	208	na	67.8 ± 9.2	141 (67.8%)
Barone et al. 2009	Italy	CS	1072	na	67.4 ± 9.4	647 (60.4%)
Bostantjopoulou et al. 2013	Greece	CS	166	66	59.5 ± 9.3	109 (66.5%)
Bulpitt et al. 1985.	UK	CS	181	263	65.0	103 (57%)
Cersosimo et al. 2011	Argentine	CS	97	86	64.1 ± 8.2	53 (55%)
Cersosimo et al. 2013	Argentine	CS	129	120	64.69 ± 8.75	68 (53%)
Chaudhuri et al. 2006	N=5	CS	123	96	68.1 ± 10.3	73 (59.3%)
Cheon et al. 2008	Korea	CS	54	na	64.9 ± 8.6	28 (38%)
Clifford and Finnerty, 1995	UK	CS	228	na	?	121 (53%)
Duncan et al. 2014	UK	CS	158	99	66.5 ± 10.3	104 (65.8%)
Edwards et al. 1993	USA	CS	56	33	67.4	41 (73%)
Fereshtehnejad et al. 2017	Sweden	Cohort	314	na	64.7 ± 9.9	193 (61.5%)
Garg et al. 2020	India	CS	50	50	57.6 ± 6.7	31 (62%)
Giorelli et al. 2014	Italy	CS	31	na	69.1 ± 8.18	22 (71%)
Guo et al. 2013	China	CS	616	na	61.8 ± 11.8	347 (56%)
Kalf et al. 2011	Netherlands	CS	104	na	68 ± 9.4	72 (69%)
Karakoc et al. 2016	Turkey	CS	63	na	65.8 ± 10.3	44 (70%)
Khoo et al. 2013	UK	CS	159	99	66.6 ± 10.3	105 (66%)
Leibner et al. 2009	USA	CS	58	51	69.27 ± 5.17	?
Malek et al. 2016	UK	CS	1738	na	67.6 ± 9.3	1132 (65.1%)
Mao et al. 2017	China	CS	586	na	65.05 ± 9.81	347 (59%)
Martinez-Martin et al. 2011	N=10	CS	411	na	64.48 ± 9.92	252 (61.31%)
Mito et al. 2020	Japan	CS	35	na	71.9 ± 7.2	14 (40%)
Moreira et al. 2017	Brasil	CS	100	na	?	50 (50%)
Mukhtar et al. 2018	Pakistan	CS	85	na	57.61 ± 10.64	70 (82%)
Muller et al. 2011	Norway	CS	207	175	67.9	122 (58,9%)
Nienstedt et al. 2017	Germany	CS	119	32	68.9 ± 10.1	80 (67%)
Ou et al. 2015	China	CS	518	na	61.94 ± 10.66	?

Duration disease [M±SD]	Disease severity MDS-UPDRS (scale III)	Disease severity HY scale	APM [Y/N]	LEDD (mg/day±SD)	Salivary type [D/ DM/ DDM]	Measurement tool
6.55 ± 6.83	?	?	Y	?	DDM	MDS-UPDRS/?
10.11 ± 6.7	29.07 ± 16.3	2.29 ± 0.75	Y	?	D	NMSQ
10.1 ± 5.4	?	2.6 ± 0.9	?	?	DDM	Saq
8.0 ± 4.3	12.0 ± 8.8*	?	Y	661.2 ± 376.7	DM	Saq
9.0 ± 4.0	13.0 ± 9.0*	?	Y	680 ± 385	DM	SAq
8 ± 5	?	?	Y	622 ± 373	DDM	SAq
9.5 ± 6.4	17.5 ± 8.6*	?	Y	820.5 ± 541.8	DDM	MDS UPDRS/SAq
8.8 ± 6.2	23.2 ± 11.3	2.30 ± 0.26	Y	551 ± 337	D	SCS-PD
5.1	24.2 ± 13.1	2.0	Y	?	D	NMSQ
7.09 ± 5.31	?	2.35 ± 0.29	Y	506.19 ± 250.2	D	NMSQ
?	?	?	Y	?	DDM	SAq
9.2 ± 5.9	21.6 ± 7.9	1.91 ± 0.10	Y	690 ± 268	DDM	SAq
7.91 ± 5.82	22.15 ± 8.54	2.21 ± 0.46	Y	700.39 ± 271.28	DDM	SAq
6.4 ± 4.3	?	2.5	Y	?	D	NMSQ
6.4 ± 6.1	?	?	Y	?	D	NMSQ
?	?	?	?	?	DM	SAq
0.53 ± 0.5	27.1 ± 12	1.98 ± 0.22	Y	176.6 ± 146.7	D	NMSQ
?	?	2.4	Y	?	D	SAq
6.6 ± 5.5	21.7 ± 12.3	?	?	?	D	MDS-UPDRS
2.64 ± 1.3	30.7 ± 12.2	2.24 ± 0.33	Y	745.1 ± 430.2	D	SCOPA-AUT
?	27.06 ± 12	2.0	Y	?	D	NMSQ
4.5 ± 4.2	28.1±14.0	2.5 ± 0.9	Y	342.5 ± 222.4	D	NMSS
10 ± 5.4	31 ± 9.8	2.42 ± 0.74	?	?	D	MDS UPDRS ROMP-saliva
5.4 ± 4.6	?	2.33 ± 0.53	Y	513.9 ± 284.6	D	MDS UPDRS
0.37	27.3 ± 12.1	1.99 ± 0.66	Y	177.4 ± 146.6	D	NMSQ
11 ± 8.66	30.76 ± 10.57	2.36 ± 0.17	Y	692.47 ± 544.03	D	SAq
1.3 ± 0.9	22.5 ± 12.1	1.55 ± 0.18	Y	294 ± 205	D	SCOPA-AUT
2.96	22.8	2.0	Y	238.57	D	MDS UPDRS
8.07 ± 5.75	?	2.43 ± 0.93	Y	?	D	NMSS
1.6 ± 1.2	18.0 ± 8.8	?	N	na	D	MDS-UPDRS
5.75 ± 4.34	?	2.50 ± 0.50	?	?	D	MDS-UPDRS
?	?	?	?	?	D	NMSS
2.3 ± 1.8	23.2 ± 11.3	1.9 ± 0.6	N	na	D	MDS-UPDRS
9.7 ± 7.1	31.3 ± 14.4	2.66 ± 0.91	Y	752 ± 419	D	DSFS
4.73 ± 4.10	29.49 ± 13.61	2.0 ± 1.0	Y	417.11 ± 286.66	D	MDS UPDRS

Study	Country	Design	Np [N]	Nc [N]	Age PD [M±SD]	Male gender PD [N(%)]
Owolabi et al. 2014	Nigeria	CS	80	80	61.1 ± 8.5	58 (72.5%)
Ozge et al. 2001	Turkey	CS	63	21	65.4 ± 10.1	31 (49.3%)
Paul et al. 2018	India	CS	75	35	63 ± 10.5	40 (53.3%)
Perez-Lloret et al. 2012	France	CS	419	na	69 ± 10	239 (57%)
Qin et al. 2019	China	CS	108	76	67.97 ± 8.58	59 (54.6%)
Ragab et al. 2019	Egypt	CS	41	na	57.95 ± 11.94	19 (43.3%)
Rana et al. 2013	Canada	CS	314	na	75 ± 10.58	177 (56.4%)
Rascol et al. 2020	Pakistan	CS	89	na	58.9 ± 9.5	57 (64%)
Shahid et al. 2020	USA	CS	44	24	65.6 ± 9	24 (54.5%)
Siddiqui et al. 2002	USA	CS	44	24	65.6 ± 9	24 (54.5%)
Spica et al. 2013	serbia	CS	107	na	69.1 ± 6.0	73 (68.2%)
Sung et al. 2014	Korea	CS	54	na	67.1 ± 10.3	22 (41%)
Vasile et al. 2014	Bucharest	CS	70	na	73.5 ± 8	46 (66%)
van Stiphout et al. 2018	Netherlands	CS	74	74	70.2 ± 8.8	48 (65%)
Verbaan et al. 2007	Netherlands	CS	420	150	61.1 ± 11.5	269 (64%)
van Wamelen et al. 2020	UK	cohort	728	na	65.72 ± 10.87	462 (63.5%)
Zhang et al. 2016	China	CS	454	114	61.54 ± 10.98	260 (57.3%)

Note| CS=cross sectional; Np = number of Parkinson's Disease patients; Nc= number of controls; N= numbers; M=mean; SD =standard deviation; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; HY=Hoehn & Yahr rating scale; APM = antiparkinsonian medication; LEDD= Levodopa Equivalent Daily Dosage; ? =unknown; na = not applicable; D = drooling; DM = Dry mouth; DDM= drooling and dry mouth; NMSS = Non-Motor Symptom Scale; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction; Saq = Self-administered questionnaire; NMSQ = Non-Motor Symptom Questionnaire ; PD-NMS = Parkinson's Non-Motor Symptom Questionnaire; SCS-PD = Siallorhea Clinical Scale for Parkinson's Disease; DSFS = Drooling Severity and Frequency scale; ROMP-Saliva = Radboud Oral Motor inventory for Parkinson's disease-Saliva

Duration disease [M±SD]	Disease severity MDS-UPDRS (scale III)	Disease severity HY scale	APM [Y/N]	LEDD (mg/day±SD)	Salivary type [D/ DM/ DDM]	Measurement tool
2	?	?	?	?	D	SAq
6.1 ± 5.3	35.6 ± 20.9**	2.1 ± 1.0	Y	?	D	SAq
5.12 ± 3.59	?	?	Y	554.46	D	SCS-PD
6 ± 5	?	2.0 ± 0.5	Y	?	D	MDS-UPDRS
5.03 ± 4.87	?	2.12 ± 0.24	?	?	DDM	PD-NMS/ SCOPA-AUT
2.7 ± 2.08	35.6 ± 20.15	1.71 ± 0.32	N	na	D	NMSQ
?	?	?	?	?	D	MDS-UPDRS
4.5 ± 2.26	?	?	Y	?	D	NMS
8.3 ± 6.5	?	2.1 ± 0.6	Y	?	D	SAq
8.3 ± 6.5	?	2.1 ± 0.6	Y	?	D	SAq
7.1 ± 4.4	35.1 ± 12.3	2.3 ± 0.6	Y	614.8 ± 262.7	D	NMSQ
1.23 ± 0.78	14.4 ± 10.6	1.6 ± 0.4	N	na	D	SAq
7.1 ± 4.5	?	2.70 ± 0.70	Y	?	D	NMSQ
9.1 ± 6.4	?	2.42 ± 1.17	?	?	DM	SAq
10.5 ± 6.5	?	2.50 ± 0.70	Y	657.7 ± 370.3	D	SCOPA-AUT
5.63 ± 5.08	?	2.19 ± 0.89	Y	525.19 ± 462.01	D	NMSS
4.76 ± 4.18	29.21 ± 13.76	2.35 ± 0.74	Y	415.60 ± 290.40	D	NMSS

Appendix

Appendix 1| session results of search PubMed, Embase.comWiley/Cochrane, Web of Science

PubMed Session Results (12 Feb 2021)

Search	Query	Items found
#3	#1 AND #2	659
#2	"Parkinsonian Disorders"[Mesh] OR parkinson*[tiab]	134,143
#1	"Sialorrhea"[Mesh] OR "Xerostomia"[Mesh] OR sialorrh*[tiab] OR drooling[tiab] OR xerostom*[tiab] OR hypersaliva*[tiab] OR hyposaliva*[tiab] OR hypersialorrh*[tiab] OR hyposialorrh*[tiab] OR ptyalism[tiab] OR sialosis[tiab] OR polysialia*[tiab] OR ((dry[tiab] OR dryness[tiab]) AND (mouth[tiab])) OR "oral dryness"[tiab] OR asialia*[tiab] OR "Saliva"[Mesh] OR "Salivation"[Mesh] OR saliva*[tiab]	133,700

Embase.com Session Results (12 Feb 2021)

Search	Query	Items found
#4	#3 NOT ('conference abstract'/it OR 'conference review'/it)	1,985
#3	#1 AND #2	2,565
#2	'Parkinson disease'/de OR parkinson*:ab,ti,kw	212,847
#1	'salivation disorder'/exp OR 'xerostomia'/exp OR sialorrh*:ab,ti,kw OR drooling:ab,ti,kw OR xerostom*:ab,ti,kw OR hypersaliva*:ab,ti,kw OR hyposaliva*:ab,ti,kw OR hypersialorrh*:ab,ti,kw OR hyposialorrh*:ab,ti,kw OR ptyalism:ab,ti,kw OR sialosis:ab,ti,kw OR polysialia*:ab,ti,kw OR (dry*:ab,ti,kw AND mouth:ab,ti,kw) OR 'oral dryness':ab,ti,kw OR asialia*:ab,ti,kw OR 'saliva'/exp OR 'salivation'/exp OR saliva*:ab,ti,kw	181,704

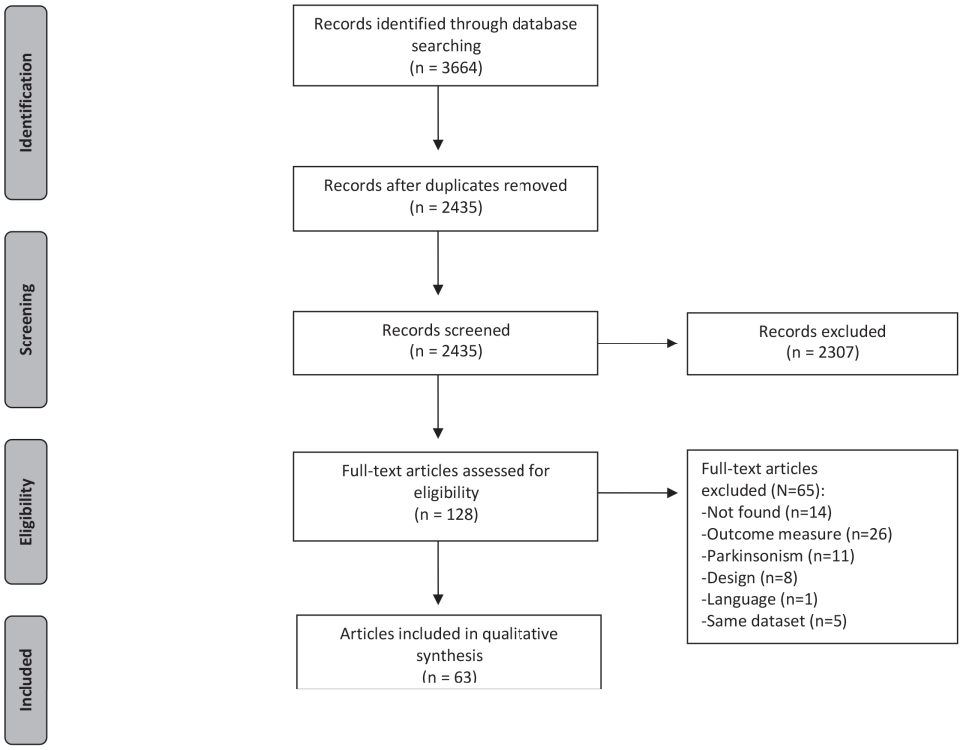
Wiley/Cochrane Library Session Results (12 Feb 2021)

Search	Query	Items found
#3	#1 AND #2	286
#2	parkinson*:ab,ti,kw	10,900
#1	sialorrh*:ab,ti,kw OR drooling:ab,ti,kw OR xerostom*:ab,ti,kw OR hypersaliva*:ab,ti,kw OR hyposaliva*:ab,ti,kw OR hypersialorrh*:ab,ti,kw OR hyposialorrh*:ab,ti,kw OR ptyalism:ab,ti,kw OR sialosis:ab,ti,kw OR polysialia*:ab,ti,kw OR (dry*:ab,ti,kw AND mouth:ab,ti,kw) OR (oral NEXT dryness):ab,ti,kw OR asialia*:ab,ti,kw OR saliva*:ab,ti,kw	17,267

Web of Science (Core Collection) Session Results (12 Feb 2021)

Search	Query	Items found
#3	#1 AND #2	734
#2	TS=(parkinson*)	181,169
#1	TS=(sialorrh* OR drooling OR xerostom* OR hypersaliva* OR hyposaliva* OR hypersialorrh* OR hyposialorrh* OR "ptyalism" OR "sialosis" OR polysialia* OR (dry* AND "mouth") OR "oral dryness" OR asialia* OR saliva*)	124,267

Appendix 2| Flowchart of the search and selection procedure of studies.



Appendix 3| The methodological quality assessment cross-sectional studies, with the Appraisal tool for Cross-Sectional Studies (AXIS tool)

Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Al-Nimer et al.2020	1	1	0	1	1	1	?	1
Aldaz et al. 2019	1	1	0	1	1	1	?	1
Anastassiadou et al. 2002	1	1	0	1	1	?	?	0
Bagheri et al.1999	1	1	0	1	1	1	?	1
Barbe et al. 2016	1	1	1	1	1	1	1	1
Barbe et al. 2016	1	1	1	1	0	0	?	1
Barbe et al. 2017	1	1	1	1	1	1	?	1
Barbe et al. 2018	1	1	1	1	1	1	?	1
Barichella et al. 2012	1	1	0	0	1	?	?	1
Barone et al.2009	1	1	0	1	1	1	0	1
Bostantjopoulou et al. 2013	1	1	0	1	1	?	?	1
Bulpitt et al. 1985	1	1	0	1	1	?	?	1
Cersosimo et al. 2009	1	1	0	1	?	?	?	1
Cersosimo et al. 2011	1	0	0	1	1	1	?	0
Cersosimo et al. 2013	1	1	0	1	1	?	?	1
Chaudhuri et al. 2006	1	1	0	1	1	1	?	1
Cheon et al.2008	1	1	0	1	?	?	?	1
Clifford and Finnerty, 1995	1	1	0	1	1	0	0	?
Duncan et al. 2014	1	0	0	1	1	1	?	1
Edwards et al. 1993	1	1	0	1	1	?	?	1
Einarsdottir et al. 2009	1	1	0	1	1	1	?	1
Fedorova et al. 2015	1	1	0	1	1	1	?	1
Fereshtehnejad et al. 2017	1	1	0	1	1	1	?	1
Fukayo et al.2003	1	1	0	1	1	0	?	1
Garg et al. 2020	1	1	0	1	1	?	?	1
Giorelli et al. 2014	1	1	0	1	1	1	?	1
Guo et al.2013	1	1	0	1	1	1	?	1
Huskic et al. 2005	1	1	0	1	1	1	?	1
Kalf et al. 2011	1	1	0	1	1	1	?	1
Karakoc et al. 2016	1	0	0	1	1	1	?	1
Khoo et al. 2013	1	1	0	1	1	1	?	1
Kusbeci et al. 2009	1	1	0	1	1	1	?	1
Leibner et al. 2009	1	1	0	1	1	?	?	1
Malek et al. 2016	1	1	0	1	1	1	?	1
Mao et al. 2017	1	1	0	1	1	1	?	1
Martinez-Martin et al. 2011	1	1	0	1	?	?	?	1
Mito et al. 2020	1	1	0	1	1	?	?	1

Q9	Q10	Q11	Q12	Q13*	Q14	Q15	Q16	Q17	Q18	Q19*	Q20	Total
1	1	1	1	0	na	1	1	1	0	?	1	15
1	1	1	1	0	na	1	1	1	1	0	1	16
0	1	0	0	0	na	0	1	0	1	?	1	9
1	1	1	0	0	na	1	1	1	0	?	1	14
1	1	1	1	0	1	1	1	1	1	?	1	19
1	1	1	1	0	na	1	1	1	1	0	1	16
1	1	1	1	0	na	1	1	1	1	?	1	17
1	1	1	1	0	na	1	1	1	1	0	1	18
1	1	1	0	0	na	1	1	1	1	0	1	14
1	1	1	1	0	1	1	1	1	1	?	1	17
1	1	1	1	0	na	1	1	0	1	0	1	15
0	1	0	0	0	na	1	1	1	0	0	?	11
1	1	0	1	0	na	1	1	0	0	?	1	11
0	1	1	1	0	na	1	0	?	1	?	1	11
?	1	1	1	0	na	1	1	1	1	0	1	15
1	1	1	1	0	na	1	1	1	1	0	1	17
1	1	1	1	0	na	0	1	1	1	0	1	14
?	0	0	0	0	na	1	1	1	1	0	0	10
1	1	1	1	0	na	1	1	1	1	?	1	15
?	1	0	1	0	na	1	1	1	0	0	?	12
1	0	0	0	0	na	1	0	1	0	?	1	11
1	1	1	1	0	na	1	1	1	1	0	1	17
1	1	1	1	0	na	1	1	1	1	0	1	17
1	1	1	0	0	na	1	1	1	1	?	?	13
1	1	1	1	0	na	1	1	1	1	0	1	16
1	0	1	1	0	na	1	1	1	1	0	1	16
1	1	1	1	0	na	1	1	1	1	0	1	17
1	1	1	0	0	na	1	0	0	0	?	?	11
1	1	1	0	0	na	1	1	1	1	0	1	16
1	1	1	1	0	na	0	0	?	1	0	1	13
1	1	1	1	0	na	1	1	1	1	0	1	17
1	1	0	1	0	na	1	1	1	0	?	1	14
0	1	1	0	0	na	1	1	1	0	?	1	12
1	1	1	1	1	1	1	1	1	1	0	1	18
1	1	1	0	0	na	1	1	1	1	0	1	16
1	1	1	1	1	1	1	1	1	1	?	1	15
1	1	1	1	0	na	1	1	1	1	0	1	16

Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Moreira et al. 2017	1	1	0	1	1	?	?	1
Mukhtar et al. 2018	1	1	1	1	1	1	?	1
Muller et al. 2011	1	1	0	1	1	1	?	1
Muller et al. 2011	1	1	0	1	1	1	?	1
Ou et al. 2015	1	1	0	1	1	?	?	1
Owolabi et al. 2014	1	1	0	1	1	?	?	1
Ozge et al. 2001	1	1	0	1	1	?	?	1
Paul et al. 2018	1	1	0	1	1	?	?	1
Perez-Lloret et al. 2012	1	1	0	1	1	0	?	1
Persson et al. 1992	1	1	0	1	1	1	?	1
Qin et al. 2019	1	1	0	1	1	?	?	1
Ragab et al. 2019	1	1	0	1	1	?	?	0
Rana et al. 2013	1	1	0	1	1	?	?	0
Rascol et al. 2020	1	1	1	1	1	?	?	1
Ribeiro et al. 2016	1	1	0	1	1	1	?	1
Shahid et al. 2020	1	1	0	1	1	?	?	1
Siddiqui et al. 2002	1	1	0	1	1	0	0	1
Spica et al. 2012	1	1	0	1	1	?	?	1
Sung et al. 2014	1	1	0	1	1	1	?	1
Tumilasci et al. 2006	1	1	0	1	1	1	?	1
van Stiphout et al. 2018	1	1	1	1	1	1	?	1
van Wamelen et al. 2020	1	1	0	1	1	1	?	1
Vasile et al. 2014	1	1	0	1	1	?	?	1
Verbaan et al. 2007	1	1	0	1	1	1	1	1
Zhang et al. 2016	1	1	0	1	1	?	?	1

Note|Q1=where the aims/objectives of the study clear?; Q2=was the study design appropriate for the stated aim(s); Q3=was the sample size justified?; Q4=was the target/reference population clearly defined? (is it clear who the research was about?); Q5=was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?; Q6=was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?; Q7=were measures undertaken to address and categorise non-responders?; Q8=were the risk factor and outcome variables measured appropriate to the aims of the study?; Q9=were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?; Q10=is it clear what was used to determining statistical significance and/or precision estimates? (e.g. p-values, confidence intervals); Q11=were the methods (including statistical methods) sufficiently described to enable them to be repeated?; Q12=were the basic data adequately described?; Q13=does the response rate raises concerns about non-responders bias?; Q14=if appropriate, was information about non-responders described?; Q15=were the results internally consistent?; Q16=were the results presented for all the analyses described in the methods?; Q17=were the author's discussions and conclusions justified by the results?; Q18=were the limitations of the study discussed?; Q19=were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?; Q20=was ethical approval or consent of participants attained?; na= not applicable

Q9	Q10	Q11	Q12	Q13*	Q14	Q15	Q16	Q17	Q18	Q19*	Q20	Total
1	1	1	0	0	na	1	1	1	1	?	1	14
1	1	1	0	0	na	0	1	1	1	0	1	16
1	1	0	1	0	na	1	1	1	1	?	1	15
1	1	1	0	1	1	1	1	1	1	?	1	16
1	1	1	0	0	na	1	1	1	1	?	1	15
?	1	0	0	0	na	1	0	1	0	?	?	9
0	1	1	1	0	na	0	1	0	1	?	1	12
1	1	1	0	0	na	1	1	1	1	0	?	14
1	1	1	0	1	1	1	1	1	1	1	1	17
1	1	0	1	0	na	1	1	1	1	0	0	15
1	1	0	1	0	na	1	1	1	0	0	1	14
1	1	1	1	0	na	1	1	1	1	0	1	15
1	1	0	0	0	na	1	0	1	1	?	1	11
1	1	1	1	0	na	1	1	1	1	0	1	17
1	1	1	1	0	na	1	1	1	?	?	1	15
1	na	1	0	0	na	1	1	1	0	?	1	12
0	1	0	0	0	na	1	1	1	1	0	1	13
1	1	1	1	0	na	1	1	1	1	0	1	16
0	1	0	1	0	na	?	1	1	0	0	1	13
1	1	1	1	0	na	1	1	1	1	0	1	17
1	1	1	1	0	na	1	1	1	1	0	1	18
1	1	1	1	0	na	1	1	1	1	0	1	17
1	1	0	0	0	na	1	0	0	1	?	1	11
1	1	1	1	1	1	1	1	1	1	0	1	19
1	1	1	1	0	na	1	1	1	1	0	1	16

Chapter 4

Oral health-related quality of life in patients with Parkinson's disease

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Abstract

Background: Parkinson's disease (PD) is a neurodegenerative condition affecting quality of life. Due to a worsening of oral health in PD patients with the progression of the disease, oral health-related quality of life (OHRQoL) could be impaired as well.

Objectives: to assess whether PD patients in The Netherlands experience worse OHRQoL than historical controls, and to investigate which factors are associated with OHRQoL in PD patients.

Material & Methods: in total, 341 PD patients (65.5 ± 8.4 years) and 411 historical controls (62.6 ± 5.3 years) participated. Both groups completed a questionnaire. The PD patients were asked questions regarding demographics, PD, oral health, and OHRQoL. The historical controls filled in demographic information and questions regarding OHRQoL. The latter construct was assessed using the Dutch 14-item version of the Oral Health Impact Profile (OHIP-14). Data were analysed using independent samples t-tests and univariate and multivariate linear regression analysis.

Results: the mean OHIP-14 score was higher in PD patients (19.1 ± 6.7) than in historical controls (16.5 ± 4.4) ($t(239)=6.5$; $p<0.001$). OHRQoL in PD patients was statistically significant associated with motor aspects of experiences of daily living ($B=0.31$; $t(315)=7.03p<0.001$), worsening of the oral environment during disease course ($B=3.39$; $t(315)=4.21p<0.001$), being dentate ($B= -5.60$; $t(315)=-4.5$; $p<0.001$), tooth wear ($B=2.25$; $t(315)=3.29$; $p=0.001$), and possible burning mouth syndrome ($B=5.87$; $t(315)=2.87$; $p=0.004$).

Conclusion: PD patients had a lower OHRQoL than historical controls. Besides, PD-related variables and oral health-related variables were associated with OHRQoL.

Keywords: Parkinson's disease; dental care for aged; oral health; quality of life; self-assessment; tooth wear.

Introduction

Parkinson's disease (PD) is a degenerative neurological condition in which dopamine levels in specific parts of the brain (e.g., striatum) are reduced [1]. Due to factors like ageing of the population [2], its estimated prevalence (currently 2 per 1,000 persons in The Netherlands) is expected to increase in the near future [3]. Although PD is well-known for its motor symptoms (e.g., tremor, rigidity, bradykinesia)[1], non-motor symptoms like depression and cognitive decline are also common, with large differences between individuals [1,4]. These different phenotypes make PD complex and difficult to manage. Although no curative treatment for PD exists so far, the symptoms can be suppressed by dopaminergic medication. Nevertheless, patients' quality of life can be reduced by the impairment and inconvenience caused by the disease [5,6]. For example, autonomic dysfunction, sleep problems, and cognitive decline are factors that can contribute to a deteriorated health-related quality of life.

Literature showed that also oral health-related quality of life could be affected bij PD. This so-called Oral Health-Related Quality of Life (OHRQoL) is defined as "a multidimensional construct that reflects factors such as people's comfort when eating, sleeping, and engaging in social interaction; their self-esteem; and their satisfaction with respect to their oral health" [7,8]. OHRQoL can be measured with several instruments (e.g., the Oral Health Impact Profile)[9–12].

A German study on OHRQoL showed that PD patients with oral symptoms like xerostomia, drooling, and dysphagia had a lower OHRQoL than PD patients without oral symptoms [13]. In addition, a weak but significant correlation was found between the OHRQoL and the duration of PD [13]. Further, a pilot study conducted in The Netherlands suggested that PD patients had a higher prevalence of temporomandibular disorder (TMD) (viz., disorders of the temporomandibular joint, masticatory muscles, and/or adjacent anatomical tissues) pain than older adults without PD[14,15]. In the literature, Da Costa Silva et al. (2015) reported that in Brazil, the OHRQoL in patients with PD with TMD[17] was worse than in PD patients without TMD [16]. However, it is still indecisive whether the OHRQoL is influenced by having PD or by TMD. Taking this evidence together, it could be speculated that PD patients have a worse OHRQoL than healthy older adults without PD. Although clinically relevant, the OHRQoL in patients with PD living in The Netherlands was not examined before. In addition, insight into the factors that are associated with the OHRQoL in PD patients is lacking.

Therefore, the aims of this study were: 1. to evaluate the OHRQoL of patients with PD as compared to that of older adults without PD; and 2. to identify factors that are associated with the OHRQoL of patients with PD. We hypothesised that, due to the expected decline of oral health and difficulties in self-care with the progression of PD, the OHRQoL of patients with PD is worse than that of older adults without PD. In addition, we hypothesised that the OHRQoL in PD patients is negatively associated with disease-related factors like the motor aspects of experiences of daily living, the duration of PD diagnosis, and a person's ability to perform oral self-care.

Material and Methods

Study design

For the first aim (viz., to compare the OHRQoL of participants with PD to that of older adults without PD), a case-control study was conducted. Data collection amongst the cases (i.e., the PD patients) was performed between June 2020 and June 2021, using an electronic questionnaire produced with Qualtrics^{XM} (SAP America Inc. Company, US) and consisting of three questionnaires, viz. 1. Self-constructed questionnaire (Appendix 1); 2. Oral Health Impact Profile (OHIP-14)[10,11] (Appendix 2); and 3. Movement Disorder Unified Parkinson's Disease Rating Scale-II (MDS-UPDRS II)[18,19] (Appendix 3). The recruitment of the cases took place through an advertisement for the electronic questionnaire on social media (e.g., Facebook, LinkedIn, and the homepage of the Dutch association of Parkinson's Disease (https://www.parkinson-vereniging.nl). Older adults without PD were added to the study as historical controls. These participants were recruited in 2013 to participate in a large epidemiological study conducted in 's-Hertogenbosch, The Netherlands (viz., a city representative of the general Dutch population regarding sociodemographic factors). In order to enable recruitment, health insurance companies were asked to provide names and addresses of their clients between 25 and 75 years of age under the authority of the National Health Care Institute (viz., Zorginstituut Nederland)[20]. The historical controls were divided by 10-years age groups to include a sufficient amount of persons per group. For the second aim (viz., to identify factors associated with the OHRQoL of patients with PD), a cross-sectional study design was used wherein only the cases of the first aim were included. The current study was approved by the Ethics Committee of the Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, The Netherlands (file no. 2020139; approval date May 26th, 2020). The large epidemiological study (i.e. regarding the historical controls) was approved by the Central Committee on Research Involving Human Subjects (CCMO) as not falling under the Medical Research Involving Human Subjects Act. Furthermore, all requirements of the Personal Data Protection Act were meet (approval No. m1501261). All participants gave their informed consent.

Participants with PD

For the PD patients, the following inclusion criteria were used: being older than 18 years of age, having PD, and having completed the electronic questionnaire. Participants who were treated with chemotherapy or radiotherapy in the head- or neck region or were diagnosed with parkinsonism were excluded. For the first aim only, PD patients of 75 years and older were excluded, because the historical control group also did not contain adults of 75 years and older.

Historical controls

The historical control group (25-74 years old) was only used for the case-control part of this study (i.e., for the study's first aim). To match the PD patients as much as possible, individuals aged 55-74 were included in the present study.

Dependent variable

For both the cases and the controls, and thus the primary and secondary aim of this study, OHRQoL was measured by means of the Dutch 14-item version of the Oral Health Impact Profile (OHIP-14)(See Appendix 2)[10,11]. This validated questionnaire consists of 14 questions with five response options, scored as follows: "Never" (score 1), "Hardly ever" (score 2), "Occasionally" (score 3), "Fairly often" (score 4), and "Very often "(score 5). A total score of 14-70 can be reached, a higher score indicating a worse OHRQoL[9–12].

Independent variables

The independent variables that were analysed for the secondairy aim of this study (viz., to determine if they have an association with the OHRQoL of PD patients) are presented in table 1. Besides, the original questionnaire used in this study, is included in the Appendix (Appendix 1).

Miscellaneous variables

In addition, to better understand the used oral hygiene methods, participants were asked which tools they use (e.g., electric toothbrush, toothpicks, dental floss) and how often they apply these methods.

Sample size calculation

To calculate the sample size for the study's second aim (i.e., with the OHIP-14 scores as an outcome variable), the software Gpower (Heinrich-Heine-Universität, Düsseldorf, Germany) was used[22]. An error of 5%, a z-score of 1.96, and a medium effect size of 0.13 for R^2 was utilised [23]. Thus, the sample size was estimated as 185 participants.

Missing data

When checking the data of PD, a technical complication was detected that had hampered the registration of gender. Therefore, after the complication was corrected, the term during which the questionnaire could be accessed was extended. Consequently, the final sample size of the PD group was more extensive than calculated (n=341). Gender was not registered in 64% of the PD patients (n=217). Therefore, getting as accurate as possible, gender was imputed based on a multiple imputation technique (viz., with in total 64 imputed datasets with ten iterations)[24].

Statistics

Descriptives were calculated for all variables. To compare the OHRQoL of PD patients with that of the historical controls, the independent samples t-test was used [20]. In addition, because the included PD patients older than 75 years of age could not be compared to the historical controls (viz., because of the age difference), an independent sample t-test was performed to see whether there is a difference in OHRQoL between the younger PD patients (74 and younger) and the older PD patients (75 and older).

To analyse which factors were associated with the OHRQoL in the PD-patient sample, a regression analysis was performed. The Variance Inflation Factor (VIF) was analysed to test for multicollinearity between the variables inserted in the regression analysis. A VIF value of 1 indicates no relation, while a VIF value above 10 shows a strong relation[25]. When a VIF value of a predictor was higher than 5, collinearity was considered present, and the predictor was excluded for the subsequent linear regression analysis[26]. We used both univariate and multiple linear regression analysis to evaluate the associations between the above-mentioned independent variables and OHRQoL. The independent variables associated with the OHRQoL ($p<0.10$) in the univariate linear regression analyses were included in the final multiple linear regression analysis. With the backward selection procedure, all independent variables with the largest p-value were step-by-step excluded until all independent variables showed a p-value equal to or lower than 0.05. The regression analysis was performed with both the original and the imputed dataset. No differences in the results were found between both datasets. Therefore, the original dataset was used. Data analysis was performed with IBM SPSS statistics (version 27.0).

Results

In total, 808 people participated in this study. There were 411 historical controls, with a mean age of 62.6 ± 5.3 years and with 50.9% having the male gender. In the PD group, 397 people filled in the questionnaire, of whom 56 participants had to be excluded because they had no PD diagnosis (n=18), and/or were treated with chemo- or radiotherapy (n=4), and/or did not complete the entire electronic questionnaire (n=38). Therefore, 341 PD patients (65.5 ± 8.4 years) were finally included in the PD group. In only 36% of the cases, gender was described (viz., 48.8% males and 51.2% females). All the descriptives of the PD patients are presented in tables 2 and 3.

The mean OHIP-14 score of PD patients (19.1 ± 6.7) was significantly higher ($t(239)=6.5$; $p<0.001$) than that of the controls (16.5 ± 4.4). Furthermore, an analysis was performed to see whether there was a difference between the younger group of PD patients (viz., <75 years of age, included in the analysis of the primary aim), and the older group of PD patients (viz., ³75 years of age, excluded in this analysis) in their OHRQoL. Although the mean OHIP-14 scores were 3 points lower in PD patients ³75 years of age (21.9 ± 9.5), compared to PD patients <75 years of age (19.1 ± 6.7), no statistically significant difference was found ($t(339)=-2.0$, $p=0.06$).

Following the second aim, he VIF of all included variables in the multiple linear regression analysis was lower than 2. Thus, no variable was excluded from the linear regression analysis based on collinearity [25,26]. The following variables showed a p-value <0.10 in the univariate linear regression analyses: age ($p<0.07$) duration of PD diagnosis ($p<0.001$), motor aspects of experiences of daily living ($p<0.001$), frequency of dental visits ($p=0.03$), worsening of oral environment during disease course ($p<0.001$), being dentate ($p<0.001$), tooth wear ($p<0.001$), possible TMD pain ($p=0.01$), possible BMS ($p<0.001$) , and drooling ($p=0.003$) (table 4). Neither in the original dataset nor in the imputed dataset, gender was found to be associated with OHRQoL. When using the multiple linear

regression analysis, only the following independent variables remained statistically significant: motor aspects of experiences of daily living (p<0.001), worsening of oral environment during disease course (p<0.001), tooth wear (p=0.001), being dentate (p<0.001), and possible BMS (p=0.004). This model explained 31% of the total variance in OHRQoL.

Discussion

The aim of the present paper was twofold: first, to evaluate the OHRQoL of patients with PD compared to that of older adults without PD; and second, to identify factors associated with the OHRQoL of patients with PD. Our results showed that PD patients had a lower OHRQoL than the historical controls. In addition, PD-related variables and oral health-related variables were positively (i.e., being dentate) and negatively (i.e., motor aspects of experiences of daily living, worsening of oral environment during disease course, having tooth wear, and having possible burning mouth syndrome) associated with OHRQoL.

Barbe et al. (2017) showed that German PD patients with oral symptoms (viz., xerostomia, drooling, and dysphagia) reported reduced OHRQoL as compared to PD patients without such symptoms [13]. Compared to the study of Barbe et al. (2017), PD patients in the present study had an even lower OHRQoL. Besides, in the current study, PD patients were also younger, had a shorter duration of their PD diagnosis, and had lower scores for motor aspects of experiences of daily living. Because of that, we expected a better OHRQoL than that reported in the study of Barbe et al., while the contrary was found. This implies that Dutch PD patients in the current study, despite a relatively mild disease rate, are experiencing a worse OHRQoL than German PD patients. In contrast to the Dutch oral health care system, German citizens are compensated for basic oral health care, which could, at least in part, explain these outcomes. This could implicate that PD patients living in The Netherlands may be deterred by the financial consequence of maintaining their oral health. When their oral health is becoming worse, their quality of life can be reduced.

Worsening of oral environment during disease course

In the present study, worsening of oral environment during disease course was associated with a reduced OHRQoL in PD patients. Van Stiphout et al. (2018) described that PD patients might experience difficulties with oral hygiene[27]. This can increase the incidence of dental pathology, resulting in, for example, dental pain and, therefore, reduced quality of life. Besides, O'Neill et al. (2021) reported a prevalence of orofacial pain in PD patients of 7.3%, associated with oral motor dysfunction[28]. Orofacial pain can greatly influence vital human needs like eating and chewing, which can have a negative impact on the quality of life of those who suffer from orofacial pain[29]. It would be logical to suggest that when people experience and report a deteriorated oral health, they would also report a worsened OHRQoL. However, in practice, when people have objectively established poor oral health, it is our experience that they do not always report having problems regarding their quality of life. Nevertheless, patients with PD in the present study did report a reduced OHRQoL. Hence, we could assume that because in PD patients quality of life is already reduced, a further

reduction due to worsening of the oral environment may affect their daily life more, compared to healthy controls without a reduced quality of life.

Self-reported tooth wear

In the literature, a poorer OHRQoL has been associated with the presence of tooth wear in the general population[30,31]. The findings of the current study confirm this negative association also in a population of PD patients. It is noteworthy to mention that, according to our clinical experience, people are not always complaining about tooth wear when the severity of the wear (i.e., the extent and amount of loss of the dental hard tissues) is mild. Therefore, it could be speculated that the severity of tooth wear is at least mild in our population, because the patients were noticing it themselves. However, no conclusion can be drawn regarding the severity of the actual, objectively established tooth wear in the studied population. In the future, it would be interesting to test whether this finding will remain significant if the tooth wear is objectively assessed during a clinical examination.

Wearing a denture

In the present study, a positive association between OHRQoL and being dentate was found. This implies that dentate persons with PD reported a significantly better OHRQoL than persons with PD who are edentulous and/or wearing a full removable prosthesis. In a study that examined both PD patients and healthy controls with partial or complete removable dentures, Ribeiro et al., 2017 found that the OHRQoL was lower in PD patients than in healthy controls[32]. However, when both groups were given new prostheses, this effect disappeared after a 2-months adaptation period, suggesting that a functional prosthesis does not negatively affect the OHRQoL. Also, in a recently published systematic review, the authors described that people who wore a denture had a 1.4 times higher chance of having a poor OHRQoL as compared to persons not wearing a denture [33]. It seems that due to all the motor effects of PD, wearing a denture can be a challenge. This can motivate people with PD to take good care of their dentition to prevent becoming edentulous. Likewise, it is also important for dental professionals to focus on preventive strategies in PD patients.

Possible burning mouth syndrome (BMS)

In the current study, a prevalence of possible BMS of 2.9% was found in older adults with PD. The literature shows a wide range (4-24%) of the prevalence of BMS in PD patients [34,35]. However, it is not certain whether there is an actual causal association between BMS and having PD. Besides, the pathophysiology undelying such an association remains unclear. In the current study, the OHRQoL was negatively associated with possible BMS in PD patients. Another questionnaire-based cross-sectional study in a healthy Swedish population supported our finding that that the presence of BMS is associated with a lower OHRQoL [36]. Since the nature of the association between BMS and PD is not evident, research should elaborate on this gap in our knowledge.

Motor aspects of experiences of daily living

The study of van Stiphout et al. (2018) showed that the disease stage of PD was negatively associated with chewing and biting problems as well as with some oral health factors (e.g., number of teeth with carious lesions, number of root remnants)[27]. Because of the design of the present study, the disease stage was not included in the collected data. However, the disease stage is most of the time established by means of the symptomatology of PD, including motor complaints. Motor aspects of experiences of daily living was one of the variables that was negatively associated with the OHRQoL in the present study. Consequently, it could be hypothesized that a negative association is present between the severity of PD and OHRQoL. PD patients in the current study were diagnosed relatively recently and were therefore relatively healthy if one considers that this disease yields no shorter lifespan for PD patients than for people without PD and that the disease course of PD has a progressive nature. This may imply that PD patients with a longer duration of their disease could experience an even worse OHRQoL. Further longitudinal studies are needed to address this aspect in the future.

Temporomandibular Disorders

In the current study, no association was found between possible TMD and the OHRQoL. In earlier studies, TMD-pain was found to be negatively associated with OHRQoL[30,36]. Furthermore, Da Costa Silva et al. (2015) showed that PD patients with TMD have a lower OHRQoL than PD patients without TMD[37]. Because an earlier pilot study suggested a higher prevalence of TMD pain in PD patients[14], and TMD pain was considered to be negatively associated with the OHRQoL[16,30,36], we assumed that in the current study the OHRQoL would be lower in PD patients. However, in contrast to the studies of Papagianni et al. (2013) and Costa da Silva et al. (2015), the methodology of the current study was based on self-report[30,37]. This could be the reason that there is a discrepancy between our results and the results described in the literature [16,30]. Therefore, a clinical assessment of TMD by means of a valid international tool like the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD)[21] is recommended for future studies.

Clinical consequences

When the OHRQoL is reduced, a person's oral health perception and the actual oral health status may be worsened. Furthermore, when the oral health status is reduced, other consequences may appear, such as difficulties in chewing, which may, in turn, be associated with factors like cognitive decline[38] and weight loss. The latter is a common problem in people affected by PD[39], and chewing difficulties may worsen that condition. Furthermore, cognitive decline is one of the non-motor symptoms that PD patients could experience. In a population that is already in need of help provided by different health care providers, the consequences of worsening of oral health could thus further increase the pressure on our health care system. To prevent that, we recommend that health care providers actively advise PD patients to seek regular oral health care and explain the urgency thereof. Besides, dental health care providers do have the task to create awareness about this topic in other domains health care. When medical doctors and dentists work together closely[40], the OHRQoL of PD patients could be preserved.

Limitations

First, this study was based on self-report, and the questionnaires were only distributed online. Due to the latter, selection bias is a possible risk because relatively healthy persons are more likely to respond to online questionnaires than more severely affected individuals. Therefore, our results could give an underestimation. Second, due to the difficulty we experienced in earlier questionnaire-based studies with correctly interpreting medication intake (e.g., the respondents' inconsistent reporting of medication types and dosages), medication usage was not asked. Hence, this factor could not be considered in our analyses. Third, due to a technical complication, most PD patients were not asked the question about gender (64%). However, the technical complication was repaired, and in the remaining 36% of the questionnaires, a 50-50 distribution was found between females and males. When imputing the missing variable (gender), no differences were found between the results of the regression analysis with the imputed datasets versus the original dataset. This is in accordance with the assumption that the missing value was at random, because the origin of the missing was a technical complication. Fourth, the study that was used to compare the OHIP-14 scores with our patient group did not contain adults of 75 years of age and older[20]. It is possible that the older adults in that category experience a worsened OHRQoL. Although in the current study no significant difference was found in that direction, the mean OHIP-14 scores were 3 points lower in PD patients <75 years of age. Because PD has no shorter life expectancy than older adults without PD, this may indicate that the OHRQoL can become even worse in this group of people. Fifth, the historical controls were not asked if they had PD[20]. Therefore, it is possible that there is a PD patient included in the historical control group and therefore an underestimation of the results is a possiblity. However, because the diagnosis is often made after several years, the chance of having a PD patient in the control group is probably the same as in studies that were asking this question directly. Besides, because of the current prevalence (viz., 2 per 1,000 persons in The Netherlands), one or two persons in the control group may have had PD. This small number is unlikely to have influenced the results of our study. Sixth, the historical controls were included during a time in which COVID19 did not exist. This contrasts with the PD patients, who were included during the first lockdown of the global pandemic. It is possible that this could have influenced our results. However, PD patients already have some distance towards society and social and professional life. Hence, the consequences of this are expected to have had a minimal influence on our results, if at all. For future studies, we recommend a longitudinal study that investigates the oral health objectively in patients with PD, along with their OHRQoL, with respect to possible associated factors (viz., medication usage, disease severity, disease stage).

Conclusion

In our study PD patients showed a lower OHRQoL than the historical controls. Besides, PD-related variables and oral health-related variables were positively (i.e., being dentate) and negatively (i.e., motor aspects of experiences of daily living, worsening of oral environment during disease course, having tooth wear, and having possible burning mouth syndrome) associated with OHRQoL. Although problems concerning oral health are probably subordinate to other problems present in

PD patients, this article suggests that the OHRQoL may be impaired in patients with PD. By being aware of this, dentists may be more alert and thus improve PD patients' oral health to prevent further deterioration of their OHRQoL.

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Tables

Table 1. Independent variables analysed for the second aim of the study (viz., to determine if the independent variables have an association with the OHRQoL of PD patients).

Variable	Question (if applicable)	Response option
Gender	What is your gender?	Male / female
Age	What is your age in years?	Years
Duration of PD diagnosis	Since how many years do you have this diagnosis?	Years
Motor aspects of experiences of daily living	Movement Disorder Unified Parkinson's Disease Rating Scale-II (MDS-UPDRS II)[18,19]	13 questions with five response options: "Normal" (score 0), "Slight" (score 1), "Mild" (score 2), "Moderate" (score 3), and "Severe "(score 4). A total score of 0-52 can be reached, a higher score indicating worse motor aspects of experiences of daily living
Living situation	What is your living situation?	Alone / with support
Frequency of dental visits	*See Appendix**	≤6 months / >6months
Frequency of brushing	*See Appendix**	<2 times a day / ≥2 times a day
Self-reported worsening of oral environment during disease course	Did you notice deterioration of your oral health during your disease?	Yes / no
Dentate	See Appendix*	Yes / no
Tooth wear	"Do you experience tooth wear?"	five response options: "No" (score 0), "Somewhat" (score 1), "Quite" (score 2), "A lot" (score 3), "Very much" (score 4), and "I don't know" (score 5). A score ≥ 1 and ≤ 4 indicates the presence of self-reported tooth wear
Possible TMD pain	"Did you ever had pain in your jaw, temple, in the ear, or in front of the ear on either side?"[21]	Yes / no
Possible burning mouth syndrome (BMS)	"Have you ever had persistent pain and/or burning sensation in your mouth the last 12 months?"	Yes / no
Drooling	MDS UPDRS II question 2 "Over the past week, have you usually had too much saliva during when you are awake or when you sleep"[18,19]	Score ≥ 2 indicated the presence of drooling
Dry mouth	"Do you experience dryness of your mouth?"	Yes / no

Note| *See Appendix 1, 2 and 3 for the detailed questionnaire and combined questions.

Table 2. Descriptives of all independent variables and the dependent variable (i.e., Oral Health-Related Quality of Life) from the participants with PD.

		Participants (n=341)
Male gender [n (%)]		60 (17.6)
	Missings	217 (63.6)
Age [M,SD (range)]		65.5 ± 8.4 (33-84)
Duration of PD diagnosis [M,SD (range)]		7.0 ± 5.5 (0-30)
Motor aspects of experiences of daily living [M, SD (range)]		11.5 ± 7.5 (0-45)
Living situation [n (%)]	Home (alone)	55 (16.1)
	Home/other (with support)	284 (83.3)
Frequency of dental visits [n (%)]	≥ 2 times a year	249 (73.0)
Frequency of brushing [n (%)]	≥ 2 times a day	248 (72.7)
Self-reported worsening of oral environment during disease course [n (%)]		81 (23.8)
Dentate [n (%)]		314 (92.1)
Tooth Wear [n (%)]		198 (58.1)
Possible TMD pain [n (%)]		49 (14.4)
Possible BMS [n (%)]		10 (2.9)
Drooling [n (%)]		154 (45,2)
Dry mouth [n (%)]		87 (25.5)
Oral Health-Related Quality of Life [M, SD (range)]	< 75 years of age	19.1 ± 6.7 (14-53)
	≥ 75 years of age	21.9 ± 9.5 (14-53)

NOTE | n = number of participants , M = mean, SD = standard deviation

Table 3. Descriptives of the miscellaneous variables from the participants with PD.

		Participants (n=341)
Autonomous self-care [n (%)]		333 (97.7)
Brushing tools [n (%)]	Manual	75 (22.0)
	Electric toothbrush or both	266 (78.0)
Interdental cleaning [n (%)]		264 (77.4)
Frequency of interdental cleaning [n (%)]	≥ 1 time a day	166 (39)
Interdental tools [n (%)]	Floss	89 (33.7)
	Toothpicks (wood)	132 (50)
	Interdental brushes (rubber)	92 (34.8)
	Interdental brushes (metal)	114 (43.2)

NOTE | n = number of participants

Table 4. Univariate and multivariate regression analyses (backward selection, with >0.05 for removal) of all independent variables with Oral Health-Related Quality of life (OHRQoL) in PD patients (n=341).

	Univariate regression analysis				Multiple linear regression analysis		
	Unstandardised coefficient	**95% C.I.**	**p-value**	**p-to-the-exit value**	**Unstandardised coefficient**	**95% C.I.**	**p-value**
Gender	1.84	1.65 – 2.03	0.18				
Age	0.09	-0.01 – 0.18	**0.07**	0.98			
Duration of PD	0.27	0.13 – 0.40	**<0.001**	0.82			
Motor aspects of experiences of daily living	0.38	0.29 – 0.48	**<0.001**		0.31	0.23 – 0.40	<0.001
Living situation	-0.01	-2.08 – 2.06	0.99				
Frequency of dental visits	-1.91	-3.63 - -0.19	**0.03**	0.76			
Frequency of brushing	-0.97	-2.70 – 0.76	0.27				
Self-reported worsening of oral environment during disease course	4.43	2.69 – 6.18	**<0.001**		3.39	1.80 – 4.97	<0.001
Dentate	-7.05	-9.80 - -4.30	**<0.001**		-5.60	-8.06 – -3.14	<0.001
Tooth wear	3.29	1.77 – 4.81	**<0.001**		2.25	0.91 – 3.60	0.001
Possible TMD pain	2.88	0.71 – 5.05	**0.010**	0.74			
Possible BMS	11.50	7.11 – 15.89	**<0.001**		5.87	1.84 – 9.90	0.004
Drooling	1.06	0.43 – 1.70	**0.001**	0.68			
Dry mouth	0.31	-1.45 – 2.08	0.73				

NOTE | R=0.56 , R^2=0.31 , C.I. = confidence interval, bold = p<0.10 and included in multivariable regression model

Appendix

Appendix 1| Questionnaire

Disclaimer: This questionnaire was originally presented in Dutch. This questionnaire has also been translated into English for transparency and reproducibility; both languages are presented (viz., Dutch in italic font).

Part 1: Self-constructed questionnaire

- Do you give permission to use your answers for scientific purposes? (*Geeft u toestemming om de ingevulde gegevens te gebruiken voor wetenschappelijk onderzoek?)*
  Yes (*Ja)* / No (*Nee)*
- What is your age in years? *(Wat is uw leeftijd in jaren?)*
- What is your gender? *(Wat is uw gender?)*
  Male *(Man)* / Female *(Vrouw)*
- How did you find out about this research? (Hoe bent u met dit onderzoek in aanraking gekomen?)
  Social Media *(Sociale Media)* / Parkinson Café *(Parkinson Café)* / The Association of PD *(Parkinson Vereniging)* / Different, namely .. *(Anders, namelijk..)*
- What is your living situation? *(Wat is uw woonsituatie?)*
  Home (alone) *(Thuis (alleen))* / Home (with partner and/or family members) *(Thuis (met partner en/of familieleden))* / Nursing home *(Verpleeghuis)* / Different, namely … *(Anders, namelijk…)*
- Do you have the diagnosis "Parkinson's disease"?
  (Heeft u de diagnose "ziekte van Parkinson"?)
  No *(Nee)* / No, I have Parkinsonism *(Nee, ik heb Parkinsonisme)* / Yes *(Ja)*
- Since how many years do you have this diagnosis? *(Hoeveel jaar/jaren heeft u de diagnose)?*
- Do you go to the dentist? *(Gaat u naar de tandarts?)*
  No *(Nee)* / Yes, when having complaints *(Ja, bij klachten)* / Yes, every … months (fill in) *(Ja, elke .. maanden (vul in))*
- Do you go to the dental hygienist? *(Gaat u naar de mondhygiënist?)*
  No *(Nee)* / Yes, every … months (fill in) *(Ja, elke … maanden (vul in))*
- Did you notice deterioration of your oral health during your disease? *(Heeft u zelf merkbare achteruitgang van uw gebit ondervonden tijdens het ziekteproces?)*
  No *(Nee)* / Yes *(Ja)* / I don't know *(Dat weet ik niet)*
- How many natural teeth/molars do you have? *(Hoeveel natuurlijke tanden/kiezen heeft u?)*
  No natural teeth *(Geen natuurlijke tanden/kiezen)* / 1-9 natural teeth *(1-9 natuurlijke tanden/kiezen)* / 10-19 natural teeth *(10-19 natuurlijke tanden/kiezen)* / 20 or more natural teeth *(20 of meer natuurlijke tanden/kiezen)*
- Do you wear a (partial) prosthesis? *(Draagt u een (gedeeltelijke) gebitsprothese?)*
  No *(Nee)* / Yes, a partial prosthesis in the upper jaw *(Ja, een gedeeltelijke protheses in de bovenkaak)* / Yes, a full prosthesis in the upper jaw *(Ja, een volledige prothese in de bovenkaak)* / Yes, a partial prosthesis in the lower jaw *(Ja, een gedeeltelijke prothese in de onderkaak)* / Yes, a full prosthesis in the lower jaw *(Ja, een volledige prothese in de onderkaak)*

- What kind of (partial) prosthesis do you wear in the upper jaw? *(Wat voor soort (gedeeltelijke) prothese draagt u in de bovenkaak?)*
  Resin *(Kunststof)* / Metal *(Metaal)*
- What kind of (partial) prosthesis do you wear in the lower jaw? *(Wat voor soort (gedeeltelijke) prothese draagt u in de onderkaak?)*
  Resin *(Kunststof)* / Metal *(Metaal)*
- Can you clean your teeth yourself? (Kunt u uw tanden/kiezen en/of protheses zelfstandig schoonmaken?)
  No (*Nee*) / No, but I've got help (*Nee, maar ik krijg hulp)* / Yes *(Ja)*
- What kind of toothbrush do you use? *(Wat voor sort tandenborstel gebruikt u?)*
  Manual *(Handtandenborstel)* / Electric (*Elektrische tandenborstel)* / Both *(Beide)*
- How many times a day do you brush your teeth? *(Hoe vaak poetst u uw tanden?)*
  Once a day *(1x per dag)* / Twice a day (*2x per dag*)/Different, namely .. (*Anders, namelijk .. per … (dag/week/maand) (vul het antwoord in)*)
- Do you use something to clean in-between your teeth?
  (Gebruikt u iets voor tussen de tanden?)
  No (*Nee*) / Yes, floss (*Flossdraad*) / Yes, toothpicks (*Tandenstokers (hout)*) / Yes, rubber brushes (*Ragers (rubber)*) / Yes, metal brushes (*Ragers (metaal)*)
- How many times do you clean in-between your teeth? *(Hoe vaak gebruikt u middelen tussen uw tanden?)*
  When something gets stuck (*Als er iets tussen zit*) / Weekly (*Wekelijks*)/ Once a day (*1x per dag*)/ Different, namely .. (*Anders, namelijk .. keer per .. (dag/week/maand) (vul het antwoord in)*)
- Do you experience a dry mouth? *(Heeft u wel eens last van een droge mond?)*
  No *(Nee) /* Yes *(Ja)*
- Did you ever receive treatment with radiotherapy or chemotherapy in your head/neck area? *(Bent u ooit behandeld met radiotherapie of chemotherapie in uw hoofd en/of halsstreek?*
  No *(Nee) /* Yes *(Ja)*
- Have you ever had pain in your jaw, temple, in the ear, or in front of the ear on either side?[1] *(Heeft u ooit pijn gehad in uw kaak, slaapstreek, in het oor, of vóór het oor (aan één of beide kanten)?)*
  No *(Nee) /* Yes *(Ja)*
- Have you ever had persistent pain and/or burning sensation in your mouth for the last 30 days? *(Heeft u de laatste 30 dagen een aanhoudende pijn en/of brandende sensatie in uw mond ervaren?)*
  No *(Nee) /* Yes *(Ja)*
- Do you experience tooth wear? *(Heeft u last van slijtage aan tanden en kiezen?)*
  No (*Niet*) / Slight (*Enigszins*) / Quite (*Nogal*) / Much (*Veel*) / Very much (*Erg veel*) / I don't know (*Weet ik niet*)

Appendix 2| Oral Health Impact Profile (OHIP-14)[2,3]

In the last six months *(In de afgelopen 6 maanden)*:	Never *(Nooit)*	Hardly ever *(Zelden)*	Occasionally *(Af en toe)*	Fairly often *(Tamelijk vaak)*	Very often *(Erg vaak)*
1. Have you had trouble pronouncing any words because of problems with your teeth, mouth or dentures? *(Hebt u moeilijkheden gehad met het uitspreken van bepaalde woorden vanwege problemen met uw gebit, mond of gebitsprothese?)*					
2. Have you felt that your sense of taste has worsened because of problems with your teeth, mouth or dentures? (*Hebt u het gevoel gehad dat uw smaakvermogen is afgenomen vanwege problemen met uw gebit, mond of gebitsprothese?)*					
3. Have you had painful aching in your mouth? *(Hebt u pijn in uw mond gehad?)*					
4. Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth or dentures? (*Hebt u moeite gehad om bepaald voedsel te eten vanwege problemen met uw gebit, mond of gebitsprothese?)*					
5. Have you been self-conscious because of your teeth, mouth or dentures? *(Hebt u zich onzeker gevoeld vanwege uw gebit, uw mond of gebitsprothese?)*					
6. Have you felt tense because of problems with your teeth, mouth or dentures? *(Hebt u zich gespannen gevoeld vanwege problemen met uw gebit, mond of gebitsprothese?)*					
7. Has your diet been unsatisfactory because of problems with your teeth, mouth or dentures? *(Is de samenstelling van uw voeding onbevredigend geweest vanwege problemen met uw gebit, mond of gebitsprothese?)*					

8. Have you had to interrupt meals because of problems with your teeth, mouth or dentures? *(Hebt u maaltijden moeten onderbreken vanwege problemen met uw gebit, mond of gebitsprothese?)*					
9. Have you found it difficult to relax because of problems with your teeth, mouth or dentures? *(Hebt u moeite gehad om zich te ontspannen vanwege problemen met uw gebit, mond of gebitsprothese?)*					
10. Have you been a bit embarrassed because of problems with your teeth, mouth or dentures? *(Hebt u zich een beetje opgelaten gevoeld vanwege problemen met uw gebit, mond of gebitsprothese?)*					
11. Have you been a bit irritable with other people because of problems with your teeth, mouth or dentures? *(Bent u wat prikkelbaar geweest tegen andere mensen vanwege problemen met uw gebit, mond of gebitsprothese?)*					
12. Have you had difficulty doing your usual jobs because of problems with your teeth, mouth or dentures? *(Hebt u moeite gehad dat het leven in het algemeen minder bevredigend was door problemen met uw gebit, mond of gebitsprothese?)*					
13. Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures? *(Hebt u het gevoel gehad dat het leven in het algemeen minder bevredigend was door problemen met uw gebit, mond of gebitsprothese?)*					
14. Have you been totally unable to function because of problems with your teeth, mouth or dentures? *(Hebt u totaal niet kunnen functioneren vanwege problemen met uw gebit, mond of gebitsprothese?)*					

Appendix 3| Movement Disorder Unified Parkinson's Disease Rating Scale-II (MDS-UPDRS II)[4,5]

	Normal *(Normaal)*	Slight *(Heel licht)*	Mild *(Licht)*	Moderate *(Matig)*	Severe *(Ernstig)*
1. Over the past week, have you had problems with your speech? *(Hebt u de afgelopen week problemen gehad met uw spraak?)*					
2. Over the past week, have you usually had to much saliva during when you are awake or when you sleep? (Hebt u in de afgelopen week gewoonlijk te veel speeksel in uw mond gehad wanneer u wakker was of sliep?)					
3. Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped, or blended to avoid choking? *(Hebt u in de afgelopen week gewoonlijk problemen gehad met het doorslikken van pillen of het nuttigen van maaltijden?)*					
4. Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knives, spoons, chopsticks? *(Hebt u in de afgelopen week gewoonlijk problemen gehad bij het hanteren en het gebruiken van bestek?)*					
5. Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? *(hebt u in de afgelopen week gewoonlijk problemen gehad bij het aankleden?)*					
6. Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair, or with other personal hygiene? *(Ging het wassen, douchen, scheren, tandenpoetsen, haren kammen of andere handelingen voor persoonlijke hygiëne doorgaans langzaam in de afgelopen week of had u hier hulp bij nodig?)*					

7.	Over the past week, have people usually had trouble reading your handwriting? *(Hebben mensen in de afgelopen week doorgaans moeite gehad om te lezen wat u met de hand had geschreven?)*					
8.	Over the past week, have you usually had trouble doing your hobbies or other things that you like to do? *(Hebt u in de afgelopen week gewoonlijk moeite gehad om uw hobby's te beoefenen of andere dingen te doen die u leuk vindt?)*					
9.	Over the past week, do you usually have trouble turning over in bed? *(Hebt u in de afgelopen week doorgaans moeite gehad om zicht om te draaien in bed?)*					
10.	Over the past week, have you usually had shaking or tremor? *(Hebt u in de afgelopen week doorgaans last gehad van beven?)*					
11.	Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair? *(Hebt u de afgelopen week doorgaans moeite gehad met uit bed stappen, uit een auto stappen of opstaan uit een diepe stoel?)*					
12.	Over the past week, have you usually had problems with balance and walking? (*Hebt u in de afgelopen week gewoonlijk problemen gehad met uw evenwicht of met lopen?)*					
13.	Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor? *(Hebt u het in de afgelopen week op een doorsnee dag terwijl u liep, meegemaakt dat u plotseling blokkeerde terwijl u verder wilde lopen, alsof uw voeten aan de grond vastzaten?)*					

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Chapter 5

Clinicians' view on the management of oral health in Parkinson's disease patients: a qualitative study

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Abstract

Background: due to numerous motor and non-motor symptoms, dental treatment in patients with Parkinson's Disease (PD) can be challenging. Knowledge regarding the optimal management of oral health care in PD patients is lacking.

Aim: to gain a deeper understanding of the experiences of dentists regarding treatment, organization, and education and research in oral health care for patients with PD in the Netherlands.

Material & Method: semi-structured interviews were conducted with general dentists and specialized dentists working with PD patients. A thematic analysis was performed using a framework-based approach.

Results: ten dentists participated in the study. The interviews showed that dental care in PD patients requires adaptation of the timing and length of treatment sessions and consultations. In addition, intensive preventive measures should be implemented. Dentists experienced the organization of oral health care in PD patients as bureaucratic and difficult. Moreover, differences between institutionalized PD patients and patients living at home were present (e.g., regarding financial support for dental treatment). Education and research are needed to improve PD patients' oral health. The experience level and affinity for treating PD patients positively influences confidence levels of the practitioner. Finally, points of improvement were suggested, such as protocolization of oral health care in PD patients and better conveyance to clinics.

Conclusion: managing oral health in PD patients is challenging, and interdisciplinary collaboration is needed to overcome difficulties. Reducing the bureaucratic burden and improving knowledge could help and stimulate oral health care providers to treat PD patients more effectively and, consequently, improve their oral health.

Keywords: Qualitative Research, Parkinson Disease, Oral Health, Practice Management, Education

Introduction

Parkinson's Disease (PD) is a neurodegenerative condition that involves the loss of nigral dopaminergic neurons in the brain and widespread accumulation of specific proteins in Lewy bodies[1], leading to non-motor symptoms (e.g., depression, pain, cognitive dysfunction) and motor symptoms (e.g., bradykinesia, tremor, freezing of gait).[2] PD affects 1-4% of individuals older than 60 years of age, and the incidence increases with ageing.[3] To suppress the symptoms related to PD, patients use many types of medication (e.g., dopaminergic medication, serotonin reuptake inhibitors, and specific anti-psychotics).[4]

During the past few decades, socioeconomic developments and new treatment options in dentistry have resulted in a decreasing number of edentulous patients. As a result, many older persons keep their teeth until late in life.[5] Individuals with PD are known to experience oral health problems, such as xerostomia or sialorrhea, a burning mouth, denture problems, periodontal disease, caries, and pain.[6,7] Compared to healthy controls, PD patients have a lower number of teeth, an increased amount of dental plaque, caries, and periodontal conditions, problems with chewing and swallowing, and issues with their dentures.[6,7] Altogether, these examples of worse oral health may result in social distancing and deterioration of their Oral Health-Related Quality of Life (OHRQoL).[8–10]

In The Netherlands, oral-health-related protocols for preventive strategies and dental treatments for institutionalized older individuals have recently been developed.[11] However, in practice, not every nursing home has sufficient staff to comply with these protocols.[11] Moreover, not every frail older individual is institutionalized.[12] Therefore, general dentists will often need to provide care to these non-institutionalized frail older persons, among whom PD patients. Due to their numerous symptoms, the provision of adequate oral health care to PD patients can be challenging. Moreover, a multidisciplinary approach may be required because of the complexity of the disease and the different phenotypes that can be distinguished within the PD-patient population. However, working together with other specialties can be a challenge, especially for dentists working in a general dental practice, due to, for example, barriers in interdisciplinary communication. In addition, some general dentists may lack affinity for geriatric dentistry, which may influence the extent to which they involve themselves in the provision of care for patients with PD. These challenges can lead to insufficiencies in the oral healthcare that PD patients currently receive. Furthermore, it is expected that the prevalence of PD will increase in the near future due to, for example, the ageing of the population.[3] Thus, it is plausible that more dentists will become involved in providing oral health care to older patients in general, including a greater number of patients with PD. Clearly, a properly structured healthcare system is needed to facilitate the delivery of adequate oral health care for PD patients, now and in the future. However, there are still many things unknown about the best possible organization and content of this system. To improve the oral health care of this special-needs population, the input of dental clinicians may provide valuable insights.

This study aims to gain a deeper understanding of the experiences of general and specialized dentists regarding treatment (viz., measures and prevention), organization (viz., politics; rules and regulations; accessibility; existing initiatives for, and points of improvement), and education and

research, including competence, of oral health care concerning patients with PD, in order to facilitate the development of a future standardized protocol to structure the oral healthcare system for PD patients, and to improve the current educational and research programs.

Material & Methods

Design

This study has a qualitative design in the form of semi-structured interviews. On the one hand, semi-structured interviews allow acquiring information regarding the interviewees' perspectives on pre-assessed topics; on the other hand, they allow collecting information regarding new topics brought up through the conversation. This approach gives methodological flexibility and yields more in-depth knowledge than quantitative research, such as surveys.[13]

Population and eligibility

Purposive sampling was used to select participants, based on specific criteria.[14] The eligibility criteria were as follows: (i) general dentists or specialized dentists working with PD patients, in the Netherlands; (ii) with ³ 2 years of working experience; and (iii) who treat or treated (i.e., no longer than two years ago) patients with PD. Dentists with personal or professional affiliations with the interviewer were excluded. Dentists were approached through the personal networks of staff working at the Department of Orofacial Pain and Dysfunction of the Academic Centre for Dentistry Amsterdam (ACTA). Dentists who specialized in geriatric dentistry were approached through the Dutch Association of Gerodontology (viz., Nederlandse Vereniging voor Gerodontologie). Moreover, advertisement took place through social media.

From dentists willing to participate, written informed consent was obtained. This study was approved by the Ethics Committee of ACTA (Reference number 2021-33650).

Interviews

An Interview topic guide was designed as an agenda to ensure that a systematic collection of information could be assembled. This topic guide consisted of six main themes that reflected our aims (Table 1). Before the study, A.B. and M.H. were trained by M.T., a dentist specialized in orofacial pain and dysfunction and researcher experienced in the conduct of qualitative research. In addition, two pilot interviews were performed to gain more experience before interviewing the participants.

Each interview took place at a date and location chosen by the participants. Prior to the interview, participants filled out a questionnaire with questions on their demographics and education (viz., year of birth, gender, year of graduation, place of graduation, working environment, and years of experience as a specialized dentist) (Table 2). A.B. and M.H. interviewed all participants and audio-recorded the conversations. The interview duration was approximately 45 minutes. After that, the recordings were transcribed verbatim, with any information removed that could reveal the interviewee's identity. After being transcribed, thematic analysis of each interview took place.

Analysis

Thematic analysis of acquired data was performed using a framework to identify emerging themes and concepts.[13] The analysis was carried out in the following steps: (i) each transcript was investigated for the identification of initial themes by A.B. and M.H.; (ii) conceptually related initial themes from the available interviews were grouped into main themes, each of which consisting of subthemes, by A.B., M.H., and M.V.; (iii) a thematic chart was created, in which the first column represented the main themes, under which each subtheme was presented in the second column by A.B., M.H., and M.V.; and (iv) the synthesis of the data and formulation of conclusions per subtheme, and subsequently per main theme, took place by A.B., M.H., M.V., and M.T. When new initial themes arose from the interviews, or more knowledge regarding the data led to new insights that required a different categorization, stepping backwards in the analytical process was allowed. Moreover, interviews were performed until no new themes emerged. To confirm this saturation, two more interviews were performed. For the analysis, a software program "ATLAS.ti" (Scientific Software Development GmbH, Berlin, Germany) was used to analyze the data and synthesize the results. A thematic chart with the summary of the results was created in Microsoft Excel software (Microsoft Corporation, Redmond, Washington, U.S.) (Table 3). Transcripts were not returned to the interviewees for comments or corrections, and no interviews were repeated. Although this article focuses on PD patients, some results may also be applicable to a broader population of frail older individuals.

Results

All interviews took place between October 2021 and March 2022. After interviewing eight of the twelve dentists that agreed to participate, saturation was achieved. Two more interviews were conducted, which confirmed that no new themes were brought up. Thus, full saturation was obtained and ten interviewees were included in the analyses (Table 2). Below, an overview of the results for each main theme and the respective sub-themes is presented. The summary of the results can be found in Table 3.

Treatment

Measures

The participants suggested that appropriate measures should be taken to ensure that the treatment for PD patients is feasible (Table 3). Oral health care providers should be flexible to ensure that patients with PD are as comfortable as possible to reduce the chance of difficulties during treatment (e.g., tremors). Measures that could be implemented are, for example, extended treatment time, or planning the treatment in the timeframe when patients experience the most benefit out of their dopaminergic medication. Furthermore, it should be noted that problems with dentures can occur due to dry mouth or motor problems. Finally, oral health care providers should consider treatment options like a shortened dental arch or dental implants for the (functional) rehabilitation of the masticatory system (Table 3).

Prevention

Preventive strategies are important when the oral health of patients with PD is at risk (Table 3). Not only are conventional preventive measures appropriate (e.g., 5000 ppm fluoride, and increased frequency of dental visits) but also someone's social support system could play an important role (e.g., taking over self-care) (Table 3).

Organization

Politics, rules, and regulations

Oral health care in older individuals is not an item on the political agenda (Table 3). Moreover, differences exist between oral health care for institutionalized older individuals with PD and patients living at home. For example, oral health care providers who treat PD patients are well supported when working in institutions. However, when working in the general dental office, it is difficult to get the right help and financial support for PD patients. Besides, when PD patients live at home, this can result in fragmented care in which many support systems are involved. Information about these support systems is lacking (e.g., entitlement of getting the right help; which institutions exists); thus, getting the care that PD patients need is difficult. Moreover, protocolized standard care is lacking in oral health care for PD patients. Finally, interdisciplinary collaboration is recommended. For example, one of the participants suggested that "neurologists have to refer PD patients to their general dentist when the PD diagnosis is established"; this to screen for possible oral health-related problems and to immediately start preventive strategies to ensure an as good as possible oral health. Besides, all participants expressed the need of intensified contact between all (oral) health care providers around the PD patient. (Table 3).

Accessibility

Especially patients with PD who live at home experience difficulties receiving the care they need. Indirectly, this can be due to regulations and politics. However, directly, the accessibility of oral care for PD patients is lacking (e.g., failing mobility, dependence on caregivers or family members) (Table 3). In addition, it is often unclear what the possibilities are for receiving oral health care that PD patients need (e.g., finding dentists who are willing to treat PD patients). Therefore, PD patients are often postponing treatment. Moreover, oral health is often found to be subordinate to PD-related symptoms: the interviewees often hear patients say they believe that when no problems occur, no dental visit is necessary (Table 3).

Existing initiatives for improvement

Some national initiatives were started to improve care for PD patients (Table 3). One example is "ParkinsonNet", which establishes a network of (para-)medic health care providers. These existing initiatives focus on interdisciplinary treatment, better accessibility for PD patients, and enlarging the expertise of (para-)medical health care providers. Furthermore, commercial companies, by way of their modus operandi in the market, contribute to increased attention to the need for (oral) health care in special needs groups. Although (oral) health care practitioners find it difficult to work with such companies, they improve the visibility of problems in our society (Table 3).

Points of improvement

The participants suggested some practical points to improve dental care for PD patients (Table 3). Examples are the development of protocol-based oral health care, establishing better conveyance to dental and medical clinics, and introducing a "vulnerability score" that gives insight into the need and the level of financial compensation for oral health care in PD patients (including PD patients living at home) (Table 3).

Education and Research

Competence

Encountering difficulties in treating patients with PD is present in both general practitioners and specialized dentists (Table 3). Although the specialized dentists see that general practitioners lack knowledge regarding oral health in older individuals, and especially in PD patients, they also experience less confidence themselves in understanding PD as a disease and in treating PD patients. Working interdisciplinary as a specialized dentist is considered to help overcome such uncertainties (Table 3).

Education

In the Netherlands, the Dutch Association of Gerodontology recognizes dentists as specialized dentists when a portfolio has been submitted that meets specific requirements. Also, a three-year post-graduate program exists, however, participation is not obligatory to meet the requirements, and a portfolio has to be submitted all the same. Both options for recognition give dentists more confidence in treating PD patients (Table 3). Reasons to start the post-graduate program are the desire to learn more regarding general medicine related to the older patient, and an affinity with geriatric dentistry. However, dentists experience some barriers to start the post-graduate program, such as the significant time-investment and the physical demands of working as a dentist specializing in geriatrics (Table 3).

Research

More research is needed to explore the etiology and pathophysiology of reduced oral health in PD patients, and to develop better treatment options (Table 3). In addition, research on the PD patients' and other health care providers' views on oral health in PD patients is needed (Table 3).

Discussion

This study aimed to gain a deeper understanding of the experiences of general and specialized dentists regarding treatment, organization, and education and research in oral health care for patients with PD. The results showed that dentists (viz., general and specialized dentists) are experiencing difficulties in treatment, organization, and education and research when working on oral health in PD patients.

Even though the results of the current study are based on the population of PD patients and on the specific situation in the Netherlands, they are in line with five out of six international recommendations that were recently provided by the Lancet Commission on Oral Health (Table 4)[15]: caregivers should be encouraged to participate in oral health care of PD patients (recommendation 1); measures

should be taken to improve oral health care for PD patients living at home (recommendations 2 and 4); more research is needed to improve decision making (recommendation 5); and difficulties with reimbursement of oral health in PD patients influence oral health negatively, and should be addressed (recommendations 2 and 6). Besides, a seventh recommendation was recently added by Lobbezoo & Aarab (2021, 2022) to stimulate interdisciplinary collaboration between medicine and dentistry (Table 4).[16,17], which was also in line with our current results that the participants of this qualitative research agree that interdisciplinary collaboration is needed (recommendation 7).

Treatment

The results of the present study showed that dentists need to be flexible, and that appropriate (preventive) measures should be taken to ensure that the treatment of PD patients will be feasible.

Over the past decades, losing all one's teeth has become less and less likely, which provides the (partly) dentate older individual with, amongst others, enhanced chewing ability and a better oral health-related quality of life. However, difficulties could arise when older adults still have their own teeth but cannot sufficiently provide self-care. This could, for example, result in oral inflammation, decay of teeth, and orofacial pain. Unfortunately, not every dental office is geared towards the older population (e.g., logistics, location). This causes specific difficulties in preventing the older individual's oral health from getting worse. When focusing on the PD patient, the problems may be more extensive (e.g., individual phenotype; dexterity of arms and fingers; dependence on the caregiver). When analyzing treatment options, implants may help stabilize, for example, a prosthesis. On the other hand, bruxism, a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible",[18] is a risk factor for implant failure.[19–21] Because motor symptoms in PD patients also occur in the orofacial area (e.g., dyskinesia), and bruxism is more prevalent in PD patients than in healthy controls,[22] this treatment option could therefore be a risk. However, when difficulties with a prosthesis occur, the resulting reduction in OHRQoL may further worsen the quality of life of the PD patient.[23,24] In such situations, it is not advisable that these treatment options should be excluded a priori.

Organization

The results of the present study highlight the need for: 1. a reduction of bureaucracy and workload; 2. more clarity about the organizational options for the dentist treating PD patients and for the PD patient itself; and 3. increased interdisciplinary collaboration.

Ageing of the population will be one of the causes of an exponential growth in the prevalence of PD in the near future. Moreover, older adults need intensified regular care to prevent oral health-related problems. However, the number of general dentists in the Netherlands is insufficient, let alone that there are enough dentists with an affinity for treating older adults and PD patients. Annually, the Dutch government only makes 259 training positions available, divided over four universities, for students to become dentists. This while approximately 1300-2075 candidates are applying to acquire a training position each year, indicating that dentistry is not lacking popularity amongst prospective students. It may thus be advisable to increase the number of training positions, because a structural shortage of dentists may jeopardize the life-cycle OHRQoL of PD patients in the Netherlands.[25]

Not only the shortage of dentists, and therefore the workload, is jeopardizing good-quality oral health care in PD patients, but also the ever-increasing administrative load.[26] Furthermore, the government encourage older individuals to live as long as possible in their own home,[12] although the care for institutionalized older adults is better regulated. Even older individuals with a strong social network are experiencing problems, so the situation for older adults with a low socioeconomic status is getting more and more arduous[27]. Should we, as caregivers, researchers, teachers, and politicians, not steer towards qualitatively better longevity at home?

Moreover, organizations (e.g., hospitals, dental practices, health care institutions) are focusing on the responsibility of the individual, clinical prevention, and health education of the individual - in this context the PD patient. However, these downstream interventions are insufficient for long-lasting changes. A balance should be found between upstream interventions (viz., health policy) and downstream interventions[28]. Watt et al. (2007) already draw the conclusion that psychosocial, economic, environmental, and political determinants should not be underestimated in influencing the oral health of the older individuals.[28] However, it seems like no reorganization in oral health care in older individuals – in this context the PD patient – has taken place yet.

Education and Research

The results of the present research highlight the compelling need for more studies focussing on the etiology of oral conditions and the development of better treatments for PD patients, as well as improved education with less barriers for dentists with affinity for the geriatric population.

Geriatric care, including care for PD patients, is not or only minimally included in the general dental curriculum. Therefore, students are not graduating with competence levels that exceed "learner" or "competent" regarding this topic.[29] The consequence of this could be that students will be (un) consciously incompetent in geriatric dentistry. Moreover, dentistry is one of the longest studies in the Netherlands, and substantial efforts of dental students are required for them to graduate as a dentist. Hence, because of the already large effort required to become a dentist, the threshold to start a specialization is high, even though the student may have affinity for dentistry focusing on geriatrics. Although in the Netherlands it is allowed to treat geriatric patients without a specialization, dentists may not feel competent to do so. How this aspect is organized in other countries, should be addressed in a future research project.

As mentioned above, when dentists want to differentiate as a specialist in geriatrics, there are two possibilities to do so in the Netherlands. Apart from a formal three-year post-graduate educational program including a portfolio, for dentists with sufficient clinical experience a portfolio to demonstrate their work experience may suffice. Although the first group enrolls in a structured educational program to obtain a comprehensive knowledge level, dentists in the second group often have more clinical experience in this area of interest. While this dualistic system increases educational inequality, it also gives the already small group of people interested in specialization the chance to choose an option that fits their needs and personal circumstances.

Importantly, there is a lack of good-quality research regarding oral health in PD patients. Consequently, practitioners cannot gather sufficient evidence-based information on oral health in PD patients, especially on how to treat them. Moreover, it is only a recent development that researchers are expected to share their findings with the general public (e.g., lectures on media channels). Until now, this was not common, with the consequence that neither general dental practitioners nor the general public were fully aware of the recent developments. Accordingly, the general public is not familiar with, for example, the importance of good and stable oral health. Thus, people will not be (internally) motivated to ask for the oral care they need, and oral health care providers are not stimulated to acquire knowledge based on the questions asked.

To conclude, the educational structure may not encourage specializing in geriatric dentistry, although the need for dentists to treat geriatric patients is increasing. Besides, there is little evidence on managing oral health problems of PD patients. Therefore, it is not likely that general and specialized dentists are able to collect enough evidence-based information to support their clinical decision making.

Limitations of the study and recommendations for future studies.

Some limitations of the present study have to be pointed out. First, of the ten interviewees, only one general dentist was included whereas the others were specialized. Besides, no other oral health care providers than dentists, such as dental hygienists, were approached. Since dental hygienists may see certain patients more frequently than dentists, this could have been a valuable addition. For future research, it is recommended to approach the dental team in a more extensive form. Second, the included group of interviewees is small. However, we followed the guidelines for qualitative research[13,30] and stopped including interviewees after saturation was achieved. This is a validated and approved approach, and therefore we are confident that our conclusions are valid. Third, we asked the participants to describe their experience as a general dentist and as a specialized dentist. However, during their work in general practice, which usually continues parttime while also working as a specialized dentist, their experience with treating PD patients could have developed further. Therefore, the outcome is probably an underestimation of their experience in this field of expertise.

Conclusion

The interviewees highlighted deficiencies in the Dutch oral health care system regarding treatment, organization, education and research concerning oral health care for PD patients. Mainly, education is lacking, since this topic is not well represented in the current dental curriculum. In addition, dentists' knowledge regarding oral health in PD patients is limited. Although less bureaucracy and more interdisciplinary approaches are likely to improve oral health care in PD patients, these issues represent major societal, political, and educational challenges. Furthermore, intensified and higher-quality research regarding oral health in PD patients is needed to close the knowledge gap and to increase the confidence level of general and specialized dentists.

Author contribution: MV, MT, and FL developed and designed this study. AB and MH performed and transcribed the interviews. MV, AB, and MH analyzed the interviews and discussed them with MT when applicable. MV drafted this manuscript. Finally, all authors reviewed the manuscript and approved the final version.

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Tables

Table 1. the main domains of the topic guide used to semi-structure the interviews.

Main domains	
1. Experience	The experience as a general practitioner and/or specialized dentist treating PD patients. (e.g., years of experience; how many patients with PD do you treat?; in what kind of setting do you treat PD patients?)
2. Diagnostics, treatment, and prevention	The interviewee's view on the diagnostics, prevention, and treatment planning in patients with PD. (e.g., which considerations do you make (regarding diagnostics, treatment and prevention) in patients with PD?; how do you experience interdisciplinary collaboration?)
3. Education	The interviewee's view on their received education regarding the management of oral health in PD patients, including dentistry, specialization, and refresher courses (e.g., what were your considerations to specialize or not specialize in geriatric dentistry?; what was your experience during your received education?; what are points of improvement in your opinion?)
4. Competence	The interviewee's feeling of competence regarding the management of oral health in PD patients (e.g., how do you feel about treating PD patients?; what do you think is necessary to improve confidence regarding the treatment of PD patients?)
5. Care system and politics	The interviewee's view on the current regulations and political aspects concerning oral health in PD patients (e.g., based on your opinion, what are positive aspects of the current care system and politics regarding oral health in PD patients?; do you want to see aspects differently, and if so, why and how?)
6. Professional practice	The interviewee's view on their professional practice and their view on future improvements regarding oral health in PD patients (e.g., how do you see interdisciplinary collaboration in oral health care in PD patients?; what do you need to experience enough satisfaction in your professional practice?)

Note|PD = Parkinson's Disease;

Table 2. Characteristics of the interviewees.

Participants (n=10)		
Gender [n (%)]	**Male**	2 (20%)
Age [M,SD (range)]		46.2±12.8 (27-64)
Specialized dentist [n (%)]		9 (90%)
Experience as a general dentist in years [M, SD (range)]		21.4±12.2 (3-39)
Experience as a specialized dentist in years [M, SD (range)]		9.9±5.4 (1-15)
Graduation type[‡] [n(%)]	**Portfolio**	4 (40%)
	Post-initial education	5 (50%)

Note| n= numbers; %=percentage; M=Mean; SD=Standard deviation; [‡]=in the Netherlands, two types of educational programs can be chosen to specialize in geriatric dentistry: "portfolio" or "post-initial educational program"(see results, section education).

Table 3. Main themes, subthemes, and summary of the clinicians' vision regarding these (sub-)themes

Main themes	Subthemes	Summary
Treatment	**Measures**	• Extended treatment time to give "rest, relaxation, and predictability". This reduces stress and anxiety during the treatment and thereby reduces the severity of the tremor.
		• Moment of treatment: tailored to the patient, based on medication intake and the wearing-off symptoms.
		• Medication (and sedation) could be considered in some situations to improve the feasibility of the treatment.
		• Material use: adjust your choice of materials when necessary (e.g., glass-ionomer instead of composite, direct restorations)
		• Treatment planning should be based on PD patients' health situation and prospects.
		• Preventive measures like shortened arch or treatment such as implants should be considered.
		• Difficulties concerning wearing a prosthesis are frequently present in patients with PD (e.g., dry mouth and hypersalivation due to polypharmacy, motor problems)
		• Difficulties concerning self-care is frequently present in patients with PD.
		• Treatment location is adjusted when necessary (e.g., ground floor, wide corridors, hoist availability, extra pillows).
		• Treatment at home is limited; only preventive measures and simple restorations can be performed. However, it can also contribute to a good assessment of a patient's living situation. Besides, it could be beneficial to understand and memorize the instructions.
		• Interdisciplinary collaboration, both within and outside dentistry, is needed to result in a better quality of care for PD patients.
		• GP's and SD's should be flexible (e.g., treatment environment, material use, difficult predictability of severity of the disease).
	Prevention	• If PD patients are at risk, preventive measures should be taken to reduce the risk of oral diseases (e.g., reducing the interval of oral hygiene measures and monitoring; fluoride application; 5000ppm fluoride toothpaste).
		• Caregivers could be included in the daily care when self-care is no longer feasible for the PD patient themself.
Organization	**Politics, rules and regulations**	• Oral health care for older individuals, let alone PD patients, is not scheduled on the political agenda.
		• Differences between PD patients living at home and institutionalized patients are becoming larger (e.g., financial support)
		• GP and SD are not supported when practicing dentistry in general offices; however, they are well supported with the administrational burden when practicing in special centers.
		• Information on support systems for PD patients living at home is lacking.
		• interdisciplinary work is recommended (e.g., standard referral to a dentist when PD diagnosis is made; intensifying contact between (oral) health care providers around the PD patient).
		• Nursing homes implement structural improvements to ensure better oral health care internally (e.g., "oral health care coordinator" or a GP or SD working in nursing homes).

Main themes	Subthemes	Summary
		• Protocolized standard care is lacking in oral health care of PD patients.
		• Oral care is not included in the inspection of nursing homes; when doing so, oral health care could be improved.
	Accessibility	• Patients' mobility is failing (e.g., to physically come to the general office; location itself because of stairs or parking).
		• Possibilities to receive special care is unclear (e.g., which dentists are competent in treating PD patients; finance).
		• PD patients are dependent on caregivers or family members.
		• PD patients already experience an overload of (para-)medic support.
		• Postpone treatment (e.g., oral health is subordinate to other PD-related problems; no oral health problems, no visit necessary; cognitive problems regarding organization).
		• The experience of SD is that PD patients prefer to stay with their dentists as long as possible.
	Existing initiatives for improvement	• Currently, dentists are included in a Dutch initiative called "Parkinson Net", which establishes a network of (para-)medic health care providers, to improve, for example, interdisciplinary collaboration, better accessibility for PD patients to (para-)medic health care providers, and enlarge expertise of (para-)medic health care providers.
		• Commercial companies are drawing attention to the need for (oral) health care in special needs groups. This could improve health care organisations in, for example, institutions. However, (oral) health care practitioners find it difficult to work along because of the motive of profit-seeking.
	Points of improvement	• SD urge the GPs: "When patients are not coming to the general office, call them yourself!"
		• Introducing a "vulnerability score" gives insight into the need and the level of compensation for oral health care in PD patients, including those living at home.
		• Protocol regarding oral health care in PD patients (including institutionalized PD patients and PD patients living at home).
		• Establishing better conveyance to dental and medical clinics could lower the barrier for PD patients and caregivers.
Education and research	**Competence**	• The GP lacks knowledge regarding oral health in older individuals, especially in PD patients (e.g., practical skills; paramedic therapies like speech therapy; salivary problems; medical diseases; best referral moment; and medication usage).
		• The affinity of GP regarding geriatric dentistry is associated with their knowledge level.
		• When experience is lacking, the SD experience confidence problems (e.g., knowledge; practical skills; frequency of dental visits).
		• Despite the experience of the SD, communication with PD patients when cognitive decline is present is difficult.
		• Working interdisciplinary as a SD helps overcome confidence problems and difficulties when no guideline for treating PD patients is present.

Main themes	Subthemes	Summary
	Education	• Recently, special needs groups have been integrated into the dentistry curriculum or in the post-initial program. However, in the past, this was lacking.
		• Both post-initial programs or the alternative by means of the "portfolio system" allows becoming a SD. Both paths are giving the SD more confidence in treating PD patients.
		Reasons to start the post-initial program to become a SD are: (i) the care for special needs groups is challenging; (ii) desire to learn more regarding general medicine; and (iii) affinity with geriatric dentistry.
		Reasons to not start the post-initial program to become a SD are (i) significant investment of time; and (ii) physically demanding work.
		Current post-initial programs are renewed to ensure quality.
	Research	Detailed research regarding the etiology of worse oral health in PD patients is needed (e.g., gut flora; oral bacteria; dry mouth; oral hygiene; ageing in general).
		Detailed research regarding treatment options for PD patients is needed (e.g., shortened dental arch; implants).
		Research on the PD patients' and other health care providers' views on oral health in PD patients is needed.

Note| GP = General Practitioner; SD=Specialized dentists

Table 4. Six key recommendations for the new WHO global strategy for oral health, published by the Lancet Commission on Oral Health (Benzian et al., 2021). The seventh recommendation was proposed by Lobbezoo & Aarab (2022).

1.	Inclusion and community engagement
2.	Place equity and social justice at the core
3.	Tackle sugars as a major common risk factor
4.	Embrace major system reforms
5.	Better data for decision making
6.	Close financing gaps
7.	Promoting interprofessional collaboration between medical doctors and dentists in research, education, prevention, and care provision.

Park 2

Orofacial pain and dysfunction in Parkinson's disease patients

Chapter 6

Orofacial pain and dysfunction in patients with Parkinson's disease: a scoping review

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Abstract

Background: Parkinson's disease (PD) is commonly known as a disorder that affects the smooth performance of body movements. In addition to the motor impairments, patients with PD often experience pain. Both motor impairments and pain can occur throughout the body, hence including the orofacial region. However, currently there is a lack of knowledge on the orofacial manifestations. Since orofacial pain and dysfunction can, amongst others, reduce the quality of life of patients with PD, it is important to explore the prevalence of these symptoms in the PD population.

Objective: to provide a broad overview of the relevant literature on orofacial pain and dysfunction in patients with PD. Furthermore, we aim to generate hypotheses for future research on this topic.

Databases and Data treatment: a literature search (in PubMed, Embase.com, Web of Science (Core collection), and Cochrane Library) was performed on January 20th, 2022, in collaboration with a medical librarian. In total, 7180 articles were found, of which 50 were finally included in this scoping review.

Results: in the included studies, pain (e.g., orofacial pain (N=2) and temporomandibular disorder pain (N=2)), orofacial motor dysfunction (e.g., limited jaw movements (N=10), reduced maximum muscle output (N=3), chewing difficulties (N=9), unspecified TMD (N=3), sensory disturbances (N=1)), and bruxism (N=3) were observed more often in patients with PD than in healthy controls.

Conclusion: patients with PD experience more pain in the orofacial area and more dysfunction of the masticatory system than their healthy peers.

Keywords: Parkinson's disease, oral health, review, temporomandibular joint disorders, mastication, facial pain

Introduction

Parkinson's Disease (PD) is a neurodegenerative disorder characterised by the accumulation of alpha-synuclein in Lewy Bodies[1] and neuronal loss in specific brain areas, amongst others in the substantia nigra[2]. In total, 1-4% of the adults older than 60 years of age are affected by this disease[3]. PD's most familiar clinical appearance is associated with motor symptoms, such as rigidity, tremor, and bradykinesia. However, even though non-motor features of PD are less familiar, they are also commonly present. Examples are depression, sleep disorders, cognitive dysfunction, and pain[4]. Pain in patients with PD has a prevalence ranging between 68% and 85%[5]. One of the most common types of pain in this patient group is musculoskeletal pain[5].

Orofacial pain is defined as "a frequent form of pain perceived in the face and/or oral cavity". It consists of different types of pain syndromes and/or disorders[6]. For example, temporomandibular disorders (TMD) is a collective term that embraces disorders of the temporomandibular joint, the masticatory muscles, and adjacent structures[7]. Symptoms of TMD include orofacial pain and headaches attributed to TMD, as well as dysfunction of the masticatory system, including joint sounds and limitations in the movement of the mandible[8]. Although not fully elucidated yet, the aetiology of TMD is considered multifactorial, with combinations of a host of biopsychosocial factors playing a role, amongst which bruxism[9,10]. Bruxism is defined as "a repetitive jaw-muscle activity characterised by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible"[11]. In addition, bruxism encompasses two circadian forms, namely sleep bruxism and awake bruxism[11]. Another disorder that may be accompanied with pain in the orofacial area is burning mouth disorder. It is defined as "an intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day over more than 3 months, without evident causative lesions on clinical examination and investigation"[6].

According to Mylius et al. (2021), pain in PD patients could be part of the disease itself, or could be unrelated to PD[12]. So far, knowledge on orofacial pain and dysfunction in patients with PD is limited. In a previous study that assessed self-reported complaints of orofacial pain and dysfunction in PD patients, a higher prevalence of TMD pain and sleep and awake bruxism was observed in this population[13]. In addition, lower velocity and deviated patterns of jaw movements have been observed in experimental animal studies using a primate model of PD[14] as well as in humans diagnosed with PD[15]. Furthermore, problems with mastication have been suggested to occur in association with these symptoms[16]. In the same way as oral health problems, orofacial pain and dysfunction could negatively influence Oral Health-Related Quality of Life (OHRQoL) in PD patients[17]. Although oral health problems in PD patients have not been studied extensively, they received more attention than orofacial pain and dysfunction[18–20]. We believe that more insight into both topics is essential, as to ultimately prevent orofacial problems in their broadest sense in PD patients.

Against this background, our scoping review aimed to give a broad overview of the relevant literature on the prevalence of orofacial pain and/or dysfunction in patients with PD and, whenever possible, in comparison with controls. Furthermore, we aimed to see which patient-related characteristics

are associated with orofacial pain and/or dysfunction in PD patients. Finally, we aimed to generate hypotheses for future research on this topic.

Material & Method

Search strategy

A literature search was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement (www.prisma-statement.org)[21]. To identify all relevant publications, we conducted systematic searches in the bibliographic databases PubMed, Embase.com, Clarivate Analytics/Web of Science (Core collection), and Wiley/Cochrane Library from inception to January 20th, 2022, in collaboration with a medical librarian. The following terms were used (including synonyms and closely related words) as index terms or free-text words: "Parkinsonian Disorders", "Oral health", "Oral functioning", and "Quality of Life"[20]. The reference lists of the identified articles were searched for relevant publications. Duplicate articles were excluded. The complete search strategies for all databases can be found in Appendix 1[20].

Inclusion and exclusion criteria

Studies were included if they met the following *a priori* formulated criteria: (i) inclusion of patients with a diagnosis of PD; (ii) information on oral health-related factors (viz., orofacial pain, TMD-pain, burning mouth disorder, jaw movements, maximum mouth output, chewing difficulties, unspecified TMD, non-painful TMD, sensory disturbances, and bruxism); and (iii) written in English or Dutch language. In addition, we excluded studies based on the following criteria: (i) the full text could not be retrieved, or it was not available; (ii) information on oral health-related factors other than orofacial pain or dysfunction (e.g., caries, periodontitis and dental status)[20]; and (iii) publication types that did not yielded original data (e.g., editorials and (systematic) reviews of the literature).

Study selection

Three reviewers (MV, DE, and ST) independently screened all potentially relevant titles and abstracts for eligibility. Upon completion of the screening of all titles and abstracts, two reviewers (DE and ST) independently screened the full-text articles of the included abstracts. Disagreements or doubts were dissolved through a consensus procedure with the third reviewer (MV).

Data extraction and analysis

All included studies were analysed using descriptive statistics, mainly percentages and means, including the standard deviations. In addition, all results were divided into: (i) within-group results, to analyse the results for all PD patients; and (ii) between-group results, when a control group was included and comparisons could therefore be made. As part of this procedure, the following assumptions and choices were made[21]: (i) when it was not explicitly reported, but we could reasonably assume that TMD pain was reported (e.g., pain in jaw muscles, pain related to masticatory function) and not orofacial pain as an umbrella term, data was recorded as such; (ii) when articles did not

make a clear distinction between TMD pain or dysfunction, articles were reported as "unspecified TMD"; (iii) when a distinction was made between ON- and OFF-periods (i.e., dopaminergic therapy is either working [ON] or is not working or works suboptimal [OFF]), we chose to report the prevalence in OFF-periods unless otherwise described; (iv) when chewing ability was measured with food particles or parafilm, we chose to report the objectified measurement of parafilm, unless described otherwise; (v) the maximum mouth opening was measured from the incisal edge of the maxillary central incisor to the incisal edge of the mandibular central incisor, unless reported otherwise; and (vi) when a distinction was made between right and left, the right side was reported.

Results

Search results

In total, 10315 articles were found: 497 in Cochrane Library, 4695 in embase.com, 2860 in PubMed, and 2263 in Web of Science. After removing duplicates, 7180 references remained. Following the study-selection procedure, 50 studies performed in 18 different countries and published between 1970 and 2022 were included: 5 RCTs, 27 case-control studies, 14 cross-sectional studies, and 4 case reports. The flow chart of the search and selection procedure is presented in Figure 1. In addition, the characteristics of all included studies and their participants are shown in Table 1.

Orofacial Pain

Orofacial Pain

In total, nine studies reported unspecified pain in the orofacial area[22–30], of which two included a control group[22,27]. The within-group results showed prevalences that varied between 12 and 74%. Furthermore, the between-group results of the two studies that included a control group showed significantly higher orofacial pain scores in PD patients than the controls, indicating that PD patients experience more orofacial pain than their healthy peers (Table 2)[22,27]. Both studies used the King Parkinson's Pain Scale (KPPS), an inter-rater based interview scale.

In conclusion, orofacial pain in PD patients is more prevalent than in controls.

Temporomandibular Disorder Pain (TMD pain)

Of the eleven studies that examined TMD pain[12,13,17,24,25,27–29,31-33], five studies included a control group[13,27,31,32,33]. The within-group results showed prevalences that varied between 0 and 33%. When analysing the between-group results, three of these studies showed significant differences between PD patients and controls (Table 2)[13,27,32]. Martinez-Martin et al. (2017) and Verhoeff et al. (2018) showed significantly higher TMD-pain prevalence in PD patients than in controls[13,27]. In contrast, the study of Persson et al. (1992) found a higher prevalence of myalgia (viz., during palpation) in controls than in PD patients. However, they did find a higher prevalence of fatigue in the masticatory muscles in PD patients (33%) than in controls (0.5%)[32]. Moreover, Bakke et al. (2011) and Wooten Watts et al. (1999) found more or less the same results for both groups[31,33]. Only Bakke et al. (2011) and Persson

et al. (1992) used clinical assessments to diagnose TMD pain. The other studies used the KPPS or a questionnaire. Finally, a case study described a PD patient who developed TMD pain located in her left joint, after involuntary movements involving that side of her face. After making a splint that restricted her movement, the pain disappeared (Table 4)[34].

In conclusion, TMD pain is suggested to be more prevalent in PD patients than in controls.

Burning Mouth Disorder (BMD)

Of the ten studies that examined BMD symptoms in PD patients[17,24,25,27–29,35–38], two studies included a control group[27,38]. The within-group results showed prevalences that varied between 1.7 and 30%. In addition, the between-group results showed no significantly higher prevalence of BMD symptoms in PD patients than in the control group (Table 2). However, all studies except for Gopalakrishnan et al. (2021) used self-reports to diagnose BMD. Gopalakrishnan et al. (2021) described that they used self-reports and a clinical assessments; however, what kind of clinical assessment was used was not reported. Finally, a case study and a case series described six patients with PD, who developed a burning sensation in the oral cavity, gums, and face (Table 4)[38,39].

In conclusion, the results suggest that the prevalence of BMD in a population of PD patients does not differ from that in controls.

Orofacial dysfunction

Limited jaw movements

In total, 16 studies analysed limitations in the jaw movements of PD patients[14,15,31-33,40- 50]. Out of these, twelve studies included a control group (Table 3)[14,15,31-33,40,42-46,48]. A distinction could be made between studies focussing on the amplitude of jaw movements, the self-reported difficulties PD patients experienced during jaw movements, or the velocity of the movements.

Nine studies analysed the amplitude of jaw movements[15,31,42,44,46,47,50-52]. The within-group results showed a range of 17.5mm[15] to 49.2(±6.9)mm[47] for the maximum mouth opening. The results of the between-group comparisons, available for six studies, were largely similar[14,15,31,42,43,46]. Five studies found smaller amplitudes of jaw movements in patients with PD compared to controls[14,15,31,42,43]. In contrast, Bandini et al. (2016) did not report significant differences[46]; however, they did report a smaller normalised range of opening in PD patients than in controls. Albuquerque et al. (2016) also included a control group, but they did not statistically analyse whether a difference was present[15]. Nevertheless, they reported more deviation (i.e., unsymmetrical opening of the mouth) in patients with PD than in controls.

Only two studies analysed the self-reported difficulties PD patients experience during jaw movements[32,33]. Both studies included a control group. The between-group results showed no significant group difference in the self-reported difficulties patients experience with jaw movements compared to controls.

In total, seven studies investigated the velocity of jaw movements[14,15,43-46,49], and all but one study included a control group[49]. The within-group results showed a range of 94.9(±33.4)mm/s to 188(±36) mm/s during opening. Besides, the between-group results showed significantly slower movements in PD patients than in controls[14,15,43-46,]. Although Albuquerque et al. (2016) did include a control group and found slower movements in PD patients than in controls, no statistical analysis was performed[15]. Only Robertson & Hammerstad (1996) found significantly faster jaw movements in PD patients than in the control group[43].

In conclusion, limited jaw movements and slower velocity of jaw movements are more prevalent in patients with PD than in controls.

Maximum muscle output

Four studies analysed the maximum muscle output in patients with PD (Table 3)[42,48,51,53]. The within-group results showed varying results for bite force, ranging between 13.4±6.5N and 164±96N; and for muscle thickness, ranging between 0.7±0.2cm and 1.0±0.3cm. Between-group results were reported in three studies that included a control group[42,48,53]. Patients with PD had significantly lower maximum bite force than controls[42]. Furthermore, the m. masseter is thinner in PD patients than in controls during rest and maximum voluntary contraction. However, the m. temporalis was thicker in PD patients than in controls during rest[48]. Only during maximum voluntary contraction, no statistically significant difference was found. Finally, the study of da Silva et al. (2019) showed significantly stronger electromyographic signals of the masticatory muscles during experimental chewing in PD patients than in controls[53].

In conclusion, the masticatory muscles of patients with PD tend to be thinner than those of controls. Although the bite force is lower in PD patients than in controls, the electromyographic signals tend to be higher during eating in PD patients than in controls.

Chewing difficulties

In total, eight studies analysed self-reported chewing difficulties in patients with PD (Table 3)[19,31-33,54-57]. The within-group results showed prevalences that varied between 19 and 39%. For the analysis of the between-group results, six studies that included a control group were available[19,31-33,56,57]. Four of these studies reported significantly higher prevalences of chewing difficulties in PD patients than in controls[19,31,33,57]. Although Persson et al. (1992) found no significant difference between the two groups, more chewing difficulties in PD patients were found in the ON-phase[32]. Only Massimo et al. (2020) reported the same results for both groups[56].

In addition to the prevalence of chewing difficulties, six studies reported difficulties in masticatory efficiency (i.e., the time or amount of chewing cycles needed to reduce the size of a specific food particle to be able to swallow it) and performance (i.e., an objective parameter which measured the size of food particles after a standard number of chewing cycles or the weight loss of gum (%))[31,41,42,47,51,56]. The within-group results demonstrated that patients with PD need 30 (±13.5) up to approximately 67

(±60) seconds to swallow a piece of apple[31,47]. Besides, masticatory performance analysed by means of weight loss ranged between 7.0 (±9.8) and 24.0 (±11.5)% weight loss of gum or ptical cube[31,41]. Finally, particle sizes were approximately 5.8mm after chewing [42,51]. For the between-group results, four studies that included a control group were available[31,41,42,56]. Bakke et al. (2011) found significantly worse masticatory performance in PD patients as compared to controls. Also, the efficiency was worse, albeit not significantly different[31]. Also, both studies of Ribeiro et al. (2017) found significantly worse masticatory performance in PD patients than in controls[41,42]. Only Massimo et al. (2020) found the same results for both groups[56].

Four studies investigated the masticatory cycle duration[14,42,49,51]. The within-group results ranged between 0.40 and 0.77 seconds per cycle. Only two studies included a between-group analysis, which showed significantly longer cycle duration during chewing in PD patients than in controls[14,42].

In conclusion, patients with PD have more difficulties with chewing than controls.

Unspecified TMD

In total, nine studies examined unspecified TMD (viz., no clear distinction was made between TMD pain or dysfunction) in patients with PD (Table 3)[31,47,55,56,58-62]. The within-group results showed prevalences that varied between 1.1 and 61.7%. The between-group results revealed, in all three studies, significantly more unspecified TMD in PD patients than in controls[31,56,58].

In conclusion, in studies in which no distinction was made between pain or dysfunction, unspecified TMD is more prevalent in patients with PD than in controls.

Non-painful TMD

Only three studies examined non-painful TMD[13,32,33], of which all three included a control group (Table 3). Wooten Watts et al. found significantly more joint sounds in patients with PD than in controls[33]. However, Verhoeff et al. (2018) and Persson et al. found no significant difference between both groups in the prevalence of having locks and impaired jaw function, respectively[13,32].

All three studies examined different non-painful TMD symptoms. Therefore, no conclusion can be drawn based on these studies.

Sensory disturbances

Only one study investigated sensory disturbances in patients with PD (Table 3)[31]. Bakke et al. (2011) reported that the time to recognise and discriminate shapes was slower in patients with PD compared to controls. However, this difference was not statistically significant. Besides, the number of positive identifications was almost the same in both groups[31].

No strong conclusion can be drawn based on a single study which suggests that patients with PD may have orofacial sensory disturbances.

Bruxism

Six articles investigated bruxism in patients with PD (Table 3)[13,25,32,33,63,64]. The within-group results showed prevalences that varied between 2 and 57%. Besides, four articles included a control group and were thus suitable to analyse between-group results[13,32,33,63]. Only one of these studies differentiated between the two circadian forms of bruxism, i.e., awake-related and sleep-related, and found significantly higher prevalence for both awake bruxism and sleep bruxism in patients with PD compared to controls[13]. Furthermore, Wooten Watts et al. (1999) found a higher prevalence of bruxism in patients with PD than in controls; however, this difference was not statistically significant[33]. The same study did find a higher prevalence of involuntary movements of the jaw and/or mouth in patients with PD than in controls[33]. Persson et al. (1992) did not find a significant difference between PD patients and controls; however, the prevalence of bruxism in PD patients was approximately 50% higher than the control group[32]. Moreover, Abe et al. (2013) found higher Rythmic Masticatory Muscle Activity (RMMA) indices for sleep bruxism episodes and burst in patients with PD compared to controls[63]. Finally, a case study described a case of a woman with PD who developed bruxism and tooth wear after using a (nowadays unusually high) dosage of 4.5grams of levodopa. Because the beneficial effect on her motor symptoms was so strong, no other medical treatment was used. Her teeth were protected by means of splint therapy, which stopped progressing the wear (Table 4)[65].

In conclusion, the prevalence of both circadian forms of bruxism in PD patients appears to be higher than in controls.

Associated factors with orofacial pain and/or dysfunction complaints in PD patients

Gender

Four studies analysed whether gender is associated with orofacial pain and/or dysfunction complaints in patients with PD (Table 4)[25,29,35,60]. Da Costa Silva et al. (2015) showed a higher prevalence of unspecified TMD in females compared to males[60]. However, this finding was not statistically analysed. Furthermore, O'Neill et al. (2021) found a higher prevalence of orofacial pain in females compared to males[29]. In addition, Bonenfant et al. found a higher prevalence of BMD in males than in females[25]. In contrast, Clifford et al. (1998) found a significantly higher prevalence of BMD in females than in males[35].

In conclusion, female gender appears to be associated with orofacial pain and/or dysfunction in PD patients, although the available evidence is not fully aligned.

Disease duration

Four studies analysed whether disease duration is associated with orofacial pain and/or dysfunction in PD patients (Table 4)[25,29,31,55]. O'Neill et al. (2021) found significantly more BMD with longer disease duration[29]. However, Bonenfant et al. (2016) found the same median disease duration for PD patients with and without BMD[25]. Moreover, Baram et al. (2021) found no correlation between masticatory efficiency and unspecified TMD on the one hand, and disease duration on the other[55]. Finally, lower unspecified TMD prevalences and higher self-reported chewing difficulties were found in the study by Bakke et al. (2011), when the disease duration was longer[31].

In conclusion, disease duration seems to be associated with self-reported chewing difficulties and the presence of BMD complaints.

Disease severity

Nine studies analysed whether disease severity is associated with orofacial pain and/or dysfunction (Table 4)[19,25,29,30,31,47,55,56,60,66]. Of these, six studies found significantly more orofacial pain and/or dysfunction, namely, orofacial pain, unspecified TMD, non-painful TMD, self-reported chewing difficulties, masticatory efficiency, and sensory disturbances, when disease severity was worse[19,29-31,47,55]. On the other hand, three studies found no correlation between disease severity and orofacial pain and/or dysfunction, namely the maximum mouth opening, myalgia, unspecified TMD, and masticatory efficiency on the one hand and disease severity on the other[31,56,60].

In conclusion, prevalences of orofacial pain, unspecified TMD, non-painful TMD, self-reported chewing difficulties, masticatory efficiency, and sensory disturbances are suggested to be higher when the severity of PD is worse.

Medication usage

Seven articles analysed whether medication usage is associated with orofacial pain and/or dysfunction (Table 4)[25,29,43,44,49,51,52]. Bonenfant et al. (2016) did not find an association between the LEDD (i.e., Levodopa Equivalent Daily Dosage) and the prevalence of BMD[25]. However, O'Neill et al. (2021) found higher median LEDD scores when BMD was present compared to no BMD in PD patients[29]. Moreover, O'Neill et al. (2021) found a higher median LEDD score when orofacial pain was present during grinding, compared to no pain[29].

Ribeiro et al. (2018) did not find significant associations between the maximum mouth opening during the ON-period and the OFF-period[51]. However, they found a larger range of jaw movements, higher maximum bite force, and better masticatory performance during the ON-period than the OFF-period. In contrast, Robbertson & Hammerstad (1996)[43], Robertson et al. (2001)[44], and Robertson et al. (2011)[52] found a larger maximum mouth opening during the ON-period compared to the OFF-period; however, only Robertson & Hammerstad (1996) found significant differences between both phases[43]. Finally, when analysing the velocity of the jaw movements, slower movements were found during the OFF-period compared to the ON-period in all three studies.

In conclusion, when dopaminergic therapy is working optimally (i.e., in the ON state), fewer orofacial pain and/or dysfunction complaints, such as the presence of BMD, limited jaw movements, slower jaw movements and masticatory performance, seem to be present.

Discussion

This scoping review aimed to give a broad overview of the relevant literature on the prevalence of orofacial pain and/or dysfunction in patients with PD and, when available, the comparison with controls. Furthermore, we aimed to see which patient-related characteristics are associated with orofacial pain and/or dysfunction in PD patients, and to generate hypotheses for future research on this topic. The majority of the studies showed that orofacial pain and/or dysfunction in the orofacial area are more common in PD patients than in healthy persons. Moreover, some studies found a correlation between, on the one hand, disease severity and other disease-related factors (e.g., medication usage) and, on the other hand, orofacial pain and/or dysfunction.

In this scoping review, orofacial pain and TMD pain were more common in PD patients than in healthy controls. Pain, in general, is a common problem in patients with PD. Various types of pain have been described in PD patients (e.g., musculoskeletal pain, neuropathic pain, central pain), and several classifications and diagnostic tools have been proposed[67,68]. The exact mechanisms responsible for a higher prevalence of pain in PD are largely unknown. However, it has been suggested that pain thresholds are lower in patients with PD, and that PD patients, therefore, experience more pain[69]. Recently, a validated classification system was published to analyze whether pain in PD patients is related to the disease itself, or whether it could be non-PD related pain[12]. Besides, in this classification system, a distinction was made between the three mechanisms causing pain: nociceptive, neuropathic, and neuroplastic pain. This is an important step towards understanding complicated pain mechanisms in PD patients related or unrelated to the disease itself. Besides, motor symptom fluctuations and dopaminergic medication can influence pain intensity. Whether dopaminergic medication has an antinociceptive effect or a modulatory effect in pain perception is still unclear[69]. In this scoping review, results concerning dopaminergic medication and pain are ambiguous: on the one hand, a positive association was found between the use of dopaminergic medication and pain, and on the other hand, some patients reported that the pain started after starting levodopa treatment. Moreover, in case series more pain was experienced in the OFF state. Although the evidence level of case series is low, this confirms the hypothesis that dopamine may positively affect pain mechanisms. Furthermore, after initiation of levodopa therapy, the pain thresholds of PD patients are found to be significantly, albeit temporarily, raised in comparison to controls. In contrast to the suggestion that dopamine could alleviate PD symptoms, such as pain, it is also possible that the progression of motoric PD symptoms is worse and thus accountable for more pain, despite medication usage. Unfortunately, only limited high-quality data is available on this topic. Hence, the results suggesting that dopaminergic therapy may reduce orofacial pain should be interpreted with caution. Besides, it is necessary to allow for the possibility that in PD patients also other motor symptoms could occur in the orofacial region. For example, bruxism after using levodopa could be interpreted as dyskinesia or vice versa. Therefore, it is recommended for future research, to critically investigate the possibility of shared characteristics of these orofacial motor symptoms. Future research should include medication dose as a parameter to analyse the association between dopaminergic therapy and orofacial motor symptoms in more detail. Besides, future research should focus on the possible fluctuating character of pain in the orofacial region, whether or not influenced by medication usage.

The majority of the studies included in this scoping review showed that PD patients have limited jaw movements in terms of maximum mouth opening and velocity of movements, and that chewing difficulties and unspecified TMD were also more common in PD patients than in controls. It is known that this patient group has reduced oral health[19], which could yield impaired chewing function due to loss of teeth or dental pain. It is important to mention that the consequences of impaired chewing ability are suggested to be farther reaching than difficulties with eating only. For example, impaired chewing abilities may be associated with cognitive dysfunction[70]. Besides, muscle force is lower in PD patients than in healthy controls, which was also found in the orofacial area[42,48]. An impairment of oral function could limit, for example, social activities such as having a dinner with friends or conversations with people[17]. Therefore, it is important to develop strategies to improve these limitations. Because of the clinical heterogeneity of PD and its progressive nature, this issue is complex to study. Nevertheless, some studies have assessed therapeutic strategies to reduce the limitations in jaw movements (e.g., physiotherapy, Deep Brain Stimulation [DBS], or insertion of a well-fitting removable prosthesis) and showed promising results[41,44,47,50]. For example, two studies found a significant improvement in masticatory efficiency and performance when instruction was given, or when a new well-fitting removable prosthesis was made[41,47]. In addition, the studies of Baram et al. (2020), Katsikitis & Pilowsky (1996), and Robertson et al. (2001) have shown improvement in opening and closing velocity through various therapies (e.g., physiotherapy and DBS)[44,47,50]. Therefore, by using such treatments, PD patients' oral function can be ameliorated, and hence their Oral Health-related Quality of Life can be improved[17]. (Oral) health practitioners need to acknowledge this worrisome issue that exceeds beyond the oral cavity. Therefore, inter-multidisciplinary approaches should be considered when treating patients with PD[71].

Bruxism was only described in six articles. In the majority of these articles, the probability level that bruxism is actually present (viz., according to the international bruxism consensus report)[11] did not exceed a "possible" bruxism diagnosis, i.e., based on self-report. However, assumptions were made that bruxism is more prevalent in PD patients than in healthy controls because of the hypothesis that, amongst others: (i) the dopaminergic system plays a role in both PD and bruxism; (ii) the prodromal phase of PD shows comparable characteristics during sleep as bruxism; and finally (iii) depression is more prevalent in PD patients and is also a risk factor for the presence of bruxism. More research with higher probability levels is needed to determine whether this hypothesis can be accepted and whether other factors are involved, such as disease-related variables (viz., disease duration, medication usage).

Limitations and strengths

This scoping review has several limitations. First, patients in all included studies are between 60 and 70 years of age, the average duration of the disease did not exceed 15 years, and the severity of the disease was in the majority of the included articles not higher than Hoehn & Yahr scale three (i.e., on a 5-point ordinal scale). Hence, because PD is a life-long condition and because of the progressive nature of PD, the severity of the disease was probably relatively mild. Because suggestions are made that the severity of PD could be associated with pain and dysfunction in the orofacial area,

one could reason that the reported findings represent an underestimation. Second, although this scoping review did not include a quality assessment, the majority of the included studies were of low to mid quality and were hampered by various sorts of bias (e.g., lack of transparency regarding the inclusion of participants or missing values; lacking characteristics of the study participants, such as dose of dopaminergic medication). Third, the methodology of the papers, their outcome variables, and the amount of the included articles per subject prevented us from performing a meta-analysis. Therefore, this scoping review presented the data descriptively. Fourth, not every article described how PD patients received a PD diagnosis (i.e., which criteria were taken into consideration to set the PD diagnosis). To be able to compare research on PD patients, uniformity is recommended. Fifth, when PD was present unilaterally, none of the articles mentioned which side was affected. Because the affected side reflects the pathophysiology of the degeneration in the involved hemisphere, it is possible that orofacial pain and/or dysfunction is present at that affected side as well. The prime strength of this scoping review is that it was performed in collaboration with a medical librarian who performed a systematic and extensive search in multiple databases. Therefore, this review provides a comprehensive overview of the relevant literature on this topic and thus on the gaps in the literature to be filled by future research. Sixth, limited data is available on the influence of therapeutic options for PD patients on orofacial pain and dysfunction complaints. Therefore, in the current article, we chose to only focus on the presence of orofacial pain and dysfunction, and on the possible influence of disease-related factors.

Implications

Limited high-quality studies are available on orofacial pain and dysfunction in PD patients. Notwithstanding, this literature review can serve to increase the awareness of health care providers of the problems that can be encountered in the orofacial area of PD patients. Further, it can assist to encourage collaboration between medicine and dentistry. Finally, based on the outcomes of this scoping review, new research can be designed, based on the gaps identified in the current literature on this topic.

Conclusions

In conclusion, orofacial pain and/or dysfunction are more prevalent in PD patients than in controls. Furthermore, in some studies, a correlation was found between, on the one hand, disease severity and other disease-related factors (e.g., medication use) and, on the other hand, orofacial pain and/or dysfunction. Based on our findings, a number of hypotheses could be formulated: (i) orofacial pain and/or dysfunction is more prevalent in PD patients than in controls; (ii) disease duration and severity are associated with a higher prevalence of orofacial pain and worse orofacial function in patients with PD as compared to controls; and (iii) medication, for example dopaminergic therapy, reduces the prevalence of pain, raises pain thresholds, (temporarily), and improves orofacial dysfunction in patients with PD. To test these hypotheses, we recommend designing a study that includes PD patients with a wide range of disease stages, from disease onset to advanced stages of the disease, to study whether disease duration and severity are associated with more orofacial pain and worse

orofacial function. In addition, disease-related factors (e.g., dose of dopaminergic medication) should be included in future studies to establish whether or not these factors can influence orofacial pain and/or dysfunction in PD patients. Furthermore, using validated and internationally approved diagnostic criteria (e.g., for TMD diagnosis the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD)) is highly recommended to be able to, for example, compare the results of different studies. Finally, an interdisciplinary approach is recommended to overcome bias related to the field of interest[71]. Ultimately, this could contribute to improved, individualized, and preferably preventive strategies aimed at reducing orofacial pain, dysfunction, and its consequences in PD patients.

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Figures and tables

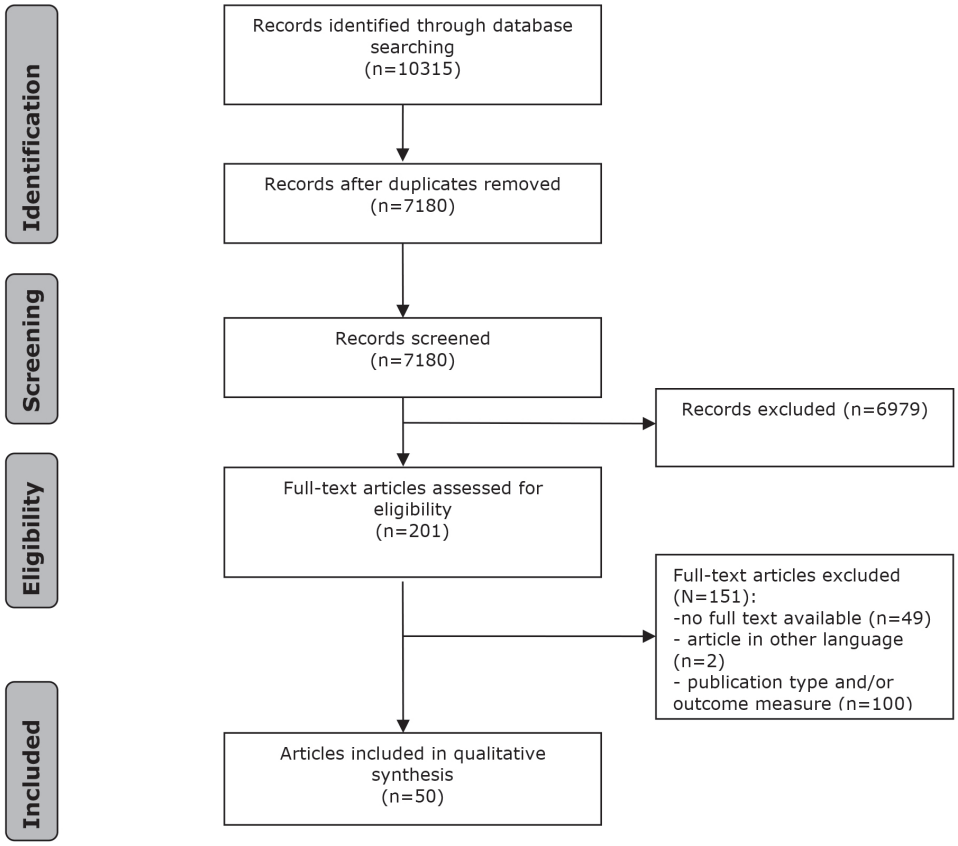

Figure 1. Flow chart of the search and selection procedure.

Table 1. Characteristics and demographics of the included studies (N=40) and participants (N=11.626).

Study	Country	Design	Np [N]	Nc [N]	Age PD M±SD [range]	Male gender PD [N(%)]
Abe et al. 2013	Canada	CC	15	9	67.1 ± 2.6	12 (80.0%)
Adachi et al. 2012	Japan	CC	3	3	N/A	3 (50.0%)
Adams et al. 2004	Canada	CC	10	10	?	?
Adewusi et al. 2018	UK	CC	51	51	68.3 ± 8.4	37 (72.5%)
Agrawal et al., 2021	India	CS	100	N/A	62 [38-85]	75 (75.0%)
Albuquerque et al. 2016	Brazil	CC	2	1	?	?
Anastassiadou et al. 2002	Greece	CS	51	N/A	67.5 ± 2.8	32 (63.0%)
Bakke et al. 2011	Denmark	CC	15	15	[61-82]	6 (40.0%)
Bandini et al. 2015	Italy	CC	14	14	71.6 ± 7.0	9 (64.3%)
Baram et al. 2020	Denmark	RCT	29	N/A	65.0 ± 10.0	15 (51.7%)
Baram et al. 2021	Denmark	RCT	29	N/A	65 [32-79]	15 (51.7%)
Barreto Tavares et al. 2021	Brazil	CS	15	N/A	69.0 ± ?	10 (66.7%)
Baumann et al. 2020	Hungary	CC	35	42	62.9 ± 9.8	?
Behari et al. 2020	India	CS	119	N/A	64.3 ± 9.6	83 (69.7%)
Bonenfant et al. 2016	Canada/France	CS	198	N/A	69.0 ± 10.3	116 (57.1%)
Choi et al. 2021	Korea	CH	6482	508383	?	2858 (47%)
Coon et al.,	USA	CR	1	-	65.0	1 (100%)
Clifford 1995	Ireland	CS	228	-	69.5#	121 (53%)
Clifford 1998	Ireland	CS	115	-	70.0 ± ?	65 (57%)
Da Silva et al. 2019	Brazil	CC	12	12	66.1 ± 3.3	?
De Mattos et al. 2019	Brazil	CS	54	N/A	66.0 ± ?	38 (70.4%)
Donizetti Verri et al. 2019	Brazil	CC	12	12	66.1 ± 3.3	?
Ford et al. 1996	USA	CR	7	N/A	70.1 ± 9.7	1 (14.3%)
Garcia et al. 2021	Spain	CH	50	N/A	68.5 ± 9.1	21 (42.0%)
Gopalakrishnan et al. 2021	India	CS	50	N/A	[30-60]	41 (82%)
Karlsson et al. 1992	Sweden	CS	12	N/A	65.0 ± ?	7 (58.3%)
Katsikitis et al. 1996	Australia	RCT	16	8	69.9 ± 5.8	7 (43.8%)
Kwak et al. 2009	Korea	CS	45	N/A	73.0 ± ?	18 (40.0%)
Magee et al. 1970	?	CR	1	N/A	53	0
Martinez-Martin et al. 2017	UK	CC	178	83	64.4 ± 11.4	38 (68.5%)
Massimo et al. 2020	Italy	CS	24	24	71.4 ± 5.9	15 (62.5%)
Minagi et al. 1998	Japan	CR	1	N/A	71	0
Mylius et al., 2021	Switzerland & Brazil	CC	159	37	65.1 ± 11.6	99 (62%)
Nakamura et al. 2013	Japan	CC	5	5	?	?
Nakayama et al. 2004	Japan	CC	104	191	?	44 (42.3%)

Duration disease M ±SD or [range]	Disease severity MDS-UPDRS (part III) M ± SD or [range]	Disease severity HY scale M ± SD or [range]	APM [Y/N]	LEDD M±SD mg/day or [range]	Outcome
5.0 ± ?	25.0 ± 2.9	3 ± ?	Y	?	BR
[0.5-0.8]	?	?	?	?	JM; CD
?	?	?	Y	?	JM
11.4 ± 6.1	?	2.0 ± ?	Y	?	OP
4.9 ± 4.1 [0-20]	15.0 ± 7.6	?	Y	414.1 ± 319.0	OP
?	?	?	?	?	JM
10.1 ± 5.4	?	2.6 ± 0.9	?	?	CD
6.7 ± 3.8	[17-61]	[2-4]	Y	?	TMD pain; JM; CD; U-TMD; SD
8.4 ± 6.1	16.0 ± 12.0	2.0 ± 0.3	Y	?	JM
11.7 ± 5.0	20.6 ± 4.9	2.9 ± 0.4	Y	?	JM; CD; U-TMD
11.7 ± 5.0	20.6 ± 4.9	2.9 ± 0.4	Y	?	CD; U-TMD
?	?	[1-3]	?	?	U-TMD
?	?	?	?	?	U-TMD
7.7 ± 5.6	15.9 ± 13.8	2.3 ± 0.9	Y	?	OP; TMD pain; BM
[6-10]	?	2.5 ± ?	Y	630.1 ± ?	OP; TMD pain; BM; BR
?	?	?	?	?	U-TMD
?	?	?	Y	[75-450]	BMD
?	?	?	?	?	BMD
?	?	?	Y	?	BMD
?	?	[1-3]	Y	?	MMO
4.0 ± ?	?	?	y	?	OP; TMD pain; BM
?	?	[1-3]	Y	?	JM; MMO
?	?	?	Y	?	BMD
6.4 ± 5.1	?	?	Y	810.2 ± 518.1	OP
?	?	?	?	?	BMD
8.0 ± ?	?	[2-4]	Y	[50-300]	JM; CD
13.5 ± 12.2	?	?	Y	?	JM
6.4 ± ?	?	?	?	?	BR (AB)
5	?	?	Y	?	BR
5.4 ± 4.9	?	2.72 ± 0.84	Y	?	OP; TMD pain; BM
?	9.4 ± 4.4	?	?	?	CD; U-TMD
3.0	?	?	Y	?	TMD pain
10.2 ± 7.6	35.5 ± 5.2	?	Y	1050 ± 635	TMD pain
?	?	?	?	?	JM
?	?	?	?	?	CD

Study	Country	Design	Np [N]	Nc [N]	Age PD M±SD [range]	Male gender PD [N(%)]
O'neill et al. 2021	UK	CH	1916	N/A	68.0 ± 9.5	1272 (65.0%)
Persson et al. 1992	Sweden	CC	30	585	73.0 ± 7.3	17 (57.0%)
Ribeiro et al. 2017a	Brazil	CS	17	17	69.4 ± 4.7	9 (52.9%)
Ribeiro et al. 2017b	Brazil	CS	17	17	69.4 ± 4.7	9 (52.9%)
Robertson et al. 2011	USA	RCT	27	27	?	25 (92.6%)
Robertson et al. 2001	USA	RCT	6	10	51.5 ± 12.0	4 (66.6%)
Robertson et al. 1996	USA	CC	8	11	53.7 ± ?	6 (75.0%)
Rodríguez-Violante et al. 2017	Mexico	CS	341	N/A	64.9 ± 12.0	182 (53.4%)
Rodrigues Ribeiro et al. 2018	Brazil	CC	11	11	73.0 ± 3.2	6 (54.6%)
Silva et al. 2015	Brazil	CS	59	N/A	65.4 ± 8.8	30 (50.8%)
Silva et al. 2016	Brazil	CS	42	N/A	61.8 ± 1.8	21 (50.0%)
van Stiphout et al. 2018	Netherlands	CC	74	74	70.2 ± 8.8	48 (65.0%)
Verhoeff et al. 2018	Netherlands	CC	395	340	67.9 ± 8.6	232 (58.7%)
Verhoeff et al. 2022	Netherlands	CC	341	411	65.5 ± 8.4	60 (17.6)
Watts et al. 1999	USA	CC	100	100	67.7 ± 9.4	?

Note| CC= case control, CS= cross-sectional, RCT=randomized controlled trial, CH=cohort study, CR=case report/ series, USA = United States of America, UK= United Kingdom, N/A= Not Applicable, %=percentage, ?= unknown, M=Mean, SD= standard deviation, LEDD=Levodopa Equivalent Daily Dosages, mg/day = milligrams per day, MDS-UPDRS=Movement Disorders Society Unified Parkinson Disease Rating Scale, H&Y=Hoehn & Yahr Scale, APM=Anti Parkinsonian Medication

Duration disease M ±SD or [range]	Disease severity MDS-UPDRS (part III) M ± SD or [range]	Disease severity HY scale M ± SD or [range]	APM [Y/N]	LEDD M±SD mg/day or [range]	Outcome
3.0 ± 2.1	?	?	Y	[400.0-465.0]	OP; TMD pain; BM
11.0 ± 5.4	?	?	Y	?	TMD pain; JM; CD; NP TMD; BR
6.8 ± 3.8	?	?	Y	?	JM; MMO; CD
6.8 ± 3.8	?	?	Y	?	CD
?	?	?	Y	?	JM
?	?	3.9 ± ?	Y	?	JM
9.0 ± ?	?	[2.5-4]	Y	?	JM
7.8 ± 5.0	29.7 ± 17.3	[1-5]	Y	674.0 ± 461.6	OP
9.8 ± 3.8	?	?	Y	?	JM; MMO; CD
7.1 ± 4.1	?	[1-3]	Y	?	U-TMD
8.7 ± 4.6	?	[1-3]	?	?	U-TMD
9.1 ± 6.4	?	2.4 ± 1.8	?	?	BM; CD
6.7 ± 5.9	?	?	Y	710.8 ± 469.8	TMD pain; NP TMD; BR
7.0 ± 5.5	?	?	?	?	TMD pain; BMD
?	?	?	?	?	TMD pain; JM; CD; NP TMD; BR

Table 2. Results for orofacial pain (viz., orofacial pain, TMD-pain, and burning mouth disorder) in patients with PD compared to controls.

Orofacial pain						
		Orofacial pain				
Article	**Method**	**Outcome measure**		**PD**	**Control**	**p-value**
Adewusi et al. 2018	RIBS (KPPS)	OFPS	M±SD	0.6±2.0	0.0±0.0	**p ≤ 0.05**
Agrawal et al. 2021	RIBS (KPPS)	OP	Prevalence	12%	N/A	N/A
Behari et al. 2020	RIBS (KPPS)	OP	Prevalence	14.8%	N/A	N/A
Bonenfant et al. 2016	SR (Quest)	OP	Prevalence	74.2%	N/A	N/A
Garcia et al. 2021	RIBS (KPPS)	OFPS	M±SD	2.5±9.6	N/A	N/A
Martinez-Martin et al. 2017	RIBS (KPPS)	OP	Prevalence	20.8%	?	?
	RIBS (KPPS)	OFPS	M±SD	1.0±3.0	0.2±1.4	**p ≤ 0.05**
de Mattos et al. 2019	RIBS (KPPS)	OP	Prevalence	7.8%	N/A	N/A
O'neill et al. 2021	RIBS (KPPS)	OP	Prevalence	7.3%	N/A	N/A
Rodriguez-Violante et al. 2017	RIBS (KPPS)	OFPS	M±SD	1.1±3.6	N/A	N/A
	RIBS (KPPS)	OP	Prevalence	17.3%	N/A	N/A
		TMD pain				
Article	**Method**	**Outcome**		**PD**	**Control**	**p-value**
Bakke et al., 2011	CA (palpation)	Myalgia	M±SD	0.2±0.4	0.1±0.3	p=0.3
Bonenfant et al. 2016	SR (Quest)	Myalgia	Prevalence	3.4%	N/A	N/A
	SR (Quest)	Artralgia	Prevalence	9.5%	N/A	N/A
Behari et al. 2020	RIBS (KPPS)	OP-chewing	Prevalence	6.5%	N/A	N/A
	RIBS (KPPS)	OP-grinding	Prevalence	3.2%	N/A	N/A
Martinez-Martin et al. 2017	RIBS (KPPS)	OP-chewing	Prevalence	8.4%	1.2%	**p ≤ 0.05**
	RIBS (KPPS)	OP-grinding	Prevalence	7.3%	2.4%	p=0.1
de Mattos et al. 2019	RIBS (KPPS)	OP-chewing	Prevalence	5.2%	N/A	N/A
	RIBS (KPPS)	OP-grinding	Prevalence	5.2%	N/A	N/A
Mylius et al. 2021	RIBS (PCS)	Myalgia	Prevalence	25.0%	N/A	N/A
O'neill et al. 2021	RIBS (KPPS)	OP-chewing	Prevalence	2%	N/A	N/A
	RIBS (KPPS)	OP-grinding	Prevalence	4%	N/A	N/A
Persson et al. 1992	SR (Quest)	OP-chewing	Prevalence	0%	0.7%	NS
	SR (Quest)	Myalgia	Prevalence	33.3%	0.5%	NS
	CA (palpation)	Myalgia	Prevalence	10%*	35%*	**p ≤ 0.01**
	SR (Quest)	Artralgia	Prevalence	0%*	10%*	NS
	SR (Quest)	OP-movement	Prevalence	6%*	5%*	NS
Verhoeff et al. 2018	SR (DC/TMD-PS)	TMD pain	Prevalence	29.5%	19.1%	**p ≤ 0.01**
Verhoeff et al. 2022	SR (DC/TMD-PS)	TMD pain	Prevalence	14.4%	N/A	N/A
Wooten Watts et al. 1999	SR (Quest)	Myalgia	Prevalence	13%	18%	NS
	SR (Quest)	TMD pain	Prevalence	3%	4%	NS

Burning Mouth Disorder						
Article	**Method**	**Outcome**		**PD**	**Control**	**p-value**
Behari et al. 2020	RIBS (KPPS)	BM	Prevalence	4.8%	N/A	N/A
	RIBS (KPPS)	BM	M±SD	0.21±1.08	N/A	N/A
Bonenfant et al. 2016	SR (Quest)	BM	Prevalence	4.0%	N/A	N/A
Clifford et al. 1995	SR (Quest)	BM	Prevalence	9.7%	N/A	N/A
Clifford et al. 1998	SR (Quest)	BM	Prevalence	24%	N/A	N/A
Gopalakrishnan et al. 2021	SR + CA (?)	BM	Prevalence	30%	N/A	N/A
Martinez-Martin et al. 2017	RIBS (KPPS)	BM	Prevalence	5.1%	1.2%	p=0.13
de Mattos et al. 2019	RIBS (KPPS)	BM	Prevalence	2.6%	N/A	N/A
O'neill et al. 2021	RIBS (KPPS)	BM	Prevalence	1.7%	N/A	N/A
Van Stiphout et al. 2018	SR (Quest)	BM	Prevalence	4.1%	0%	p=0.09
Verhoeff et al. 2022	SR (Quest)	BM	Prevalence	2.9%	N/A	N/A

Note| p= p-value, N/A= Not Applicable, NS= Not Significant, ?= unknown, SR= Self-report, CA= Clinical Assessment, M=Mean, SD= standard deviation, %=percentage, Quest= Questionnaire, OP= Orofacial Pain, OP-chewing = Orofacial Pain during chewing, OP-grinding = Orofacial Pain during grinding, OP-movement= Orofacial Pain during movement, TMD= Temporomandibular disorders, OFPS= Orofacial Pain Score, KPPS= King's Parkinson's Pain Scale, N/A= Not Applicable, ? = not described; RIBS=Rater Interview Based Scale; DC/TMD-PS=Diagnostic Criteria for Temporomandibular Disorders – Pain Screener, PCS=Parkinson's Disease Pain Classification System Questionnaire, OP-movement=Orofacial pain during movement, BM= Burning Mouth, *=estimation because of reading figure

Table 3. Results for orofacial dysfunction (viz., limited jaw movements, maximum muscle output, chewing difficulties, unspecified TMD, non-painful TMD, sensory disturbances, and bruxism) in patients with PD compared to controls.

Orofacial dysfunction						
		Limited jaw movements				
Article	**Method**	**Outcome measure**		**PD**	**Control**	**p-value**
Adams et al. 2004	CA (habitual)	Duration of jaw movement (cycles/s)	M	2.5	3	**p ≤ 0.05**
Adachi et al. 2012	CA (exp)	Movement during opening (mm)	M	18*	24*	**p ≤ 0.01**
	CA (exp)	Movement during closing (mm)	M	11*	20*	**p ≤ 0.01**
	CA (exp)	Velocity of opening (mm/s)	M	125*	200*	**p ≤ 0.01**
	CA (exp)	Velocity of closing (mm/s)	M	150*	200*	**p ≤ 0.01**
Albuquerque et al. 2016	CA (exp)	MMO (mm)	M	17.5[1]	36mm	N/A
	CA (exp)	MMO (mm)	M	38.5[2]	36mm	N/A
	CA (exp)	Velocity of MMO (mm/s)	M	213 [1]	468	N/A
	CA (exp)	Deviation of opening path (mm)	M	9.7[2]	2.7mm	N/A
Bakke et al. 2011	CA (exp)	MMO (mm)	M±SD	44.0±7.1	58.5±4.3	**p ≤ 0.01**
Bandini et al. 2016	CA (exp)	Velocity of opening (mm/s)	M±SD	94.94±33.40	64.45±30.94	**p ≤ 0.05**
	CA (exp)	Velocity of closing (mm/s)	M±SD	87.85±31.28	61.54±28.49	**p ≤ 0.05**
	CA (exp)	Normalised range of opening	M±SD	0.46±0.23	0.65±0.36	p=0.10
Baram et al. 2020	CA (exp)	MMO (mm)	M±SD	49.2±6.9	N/A	N/A
Donizetti Verri et al. 2019	CA (rest)	RMS rest (CC sEMG)	MM	0.23	0.07	**p ≤ 0.01**
	CA (exp)	RMS maximum lateral movement (CC sEMG)	MM	0.33	0.12	**p ≤ 0.01**
	CA (exp)	RMS maximum protrusion (CC sEMG)	MM	0.47	0.14	**p ≤ 0.01**
Karlsson et al. 1992	CA (exp)	Velocity of closing (mm/s)	M±SD	136±30	N/A	N/A
	CA (exp)	Velocity of opening (mm/s)	M±SD	188±36	N/A	N/A
	CA (exp)	Duration of total movement cycle (s)	M±SD	0.50±0.13	N/A	N/A
Katsikis et al. 1996	CA (habitual)	MO[3] (mm)	M±SD	15.3±5.7	N/A	N/A
Nakamura et al. 2013	CA (exp)	Duty time (%) m. masseter (for activities 5% EMG-peak)	M±SD	6.0±3.0*	5.0±1.0*	NS
	CA (exp)	Duty time (%) m. digastricus (for activities 5% EMG-peak)	M±SD	18.2±2.9%	13.1±4.7%	**p ≤ 0.05**
Persson et al. 1992	CA (exp)	Opening difficulties (<40mm)	Prevalence	25%	12.5%	**p ≤ 0.05**
	SR (Quest)	Opening difficulties	Prevalence	1%	0.7%	NS
Ribeiro et al. 2017[a]	CA (exp)	MMO (mm)	M±SD	21.9±12.7	34.8±8.6	**p ≤ 0.01**
	CA (exp)	Lateral deviation (mm)	M±SD	2.8±2.9	6.7±4.0	**p ≤ 0.01**
	CA (exp)	Maximum protrusion (mm)	M±SD	18.9±13.4	31.7±8.4	**p ≤ 0.01**
	CA (exp)	Maximum lateral right (mm)	M±SD	4.2±3.0	12.6±6.4	**p ≤ 0.01**

Ribeiro et al. 2018	CA (exp)	MMO (mm)	M±SD	31.3±3.1	N/A	N/A
	CA (exp)	Lateral deviation (mm)	M±SD	2.2±2.2	N/A	N/A
	CA (exp)	Maximum protrusion (mm)	M±SD	41.6±9.9	N/A	N/A
	CA (exp)	Maximum lateral right (mm)	M±SD	6.7±2.9	N/A	N/A
Robertson & Hammerstad 1996	CA (exp)	MMO (mm)	M±SD	28±5*	40±5*	**p ≤ 0.01**
	CA (habitual)	Velocity of opening (mm/s)	M±SD	120 ± 50*	210 ± 75*	**p ≤ 0.05**
	CA (habitual)	Velocity of closing (mm/s)	M±SD	120 ± 50*	210 ± 75*	**p ≤ 0.05**
	CA (exp)	MO (mm)	M±SD	11±4*	13±4*	NS
Robertson et al. 2001	CA (exp)	MMO (mm)	Range	17.5-42	N/A	N/A
	CA (exp)	Velocity of opening (mm/s)	Range	25-170	N/A	N/A
	CA (exp)	Velocity of opening (mm/s)	M±SD	105±10*	180±8.3	N/A
Wooten Watts et al. 1999	SR (Quest)	Opening difficulties	Prevalence	4%	4%	NS

Maximum muscle output

Article	Method	Outcome measure		PD	Control	p-value
Donizetti Verri et al. 2019	CA	Bite force (N)	M±SD	164.6±96.76	400.5±224.50	**p ≤ 0.01**
	CA (rest)	Muscle thickness, masseter (cm)	M±SD	0.78±0.20	1.00±0.16	**p ≤ 0.05**
	CA (rest)	Muscle thickness, temporalis (cm)	M±SD	0.74±0.15	0.59±0.16	**p ≤ 0.05**
	CA (MVC, electrical)	Muscle thickness, masseter (cm)	M±SD	1.02±0.28	1.38±0.15	**p ≤ 0.01**
	CA (MVC, electrical)	Muscle thickness, temporalis (cm)	M±SD	0.83±0.19	0.72±0.17	p=0.18
Ribeiro et al. 2017[a]	CA (transducer)	Bite force (N)	M±SD	89.8±25.50	157.9±77.10	**p ≤ 0.01**
Ribeiro et al. 2018	CA (transducer)	Bite force (N)	M±SD	13.4±6.50	N/A	N/A
da Silva et al. 2019	CA (parafilm)	EMG, masseter	M±SD	1.52±0.22	1.03±0.13	p=0.08
	CA (parafilm)	EMG, temporalis	M±SD	1.90±0.44	.98±0.11	**p ≤ 0.01**

Chewing difficulties

Article	Method	Outcome measure		PD	Control	p-value
Adachi et al. 2012	CA (sweet potato)	MCD (s)	M	0.39*	0.31*	**p ≤ 0.01**
Anastassiadou et al. 2002	SR (Quest)	CD	Prevalence	39%	N/A	N/A
Bakke et al. 2011	SR (Quest)	CD	M±SD	0.9±1.0	0.0±0.0	**p ≤ 0.01**
	CA (apple)	ME (s)	M±SD	67.6±57.8	34.4±4.2	p=0.10
	CA (gum)	MP (weight loss, %)	M±SD	24.0 ± 11.5%	33.5 ± 3.8%	**p ≤ 0.01**
Baram et al. 2020	CA (apple)	ME (s)	M±SD	28.4±13.5	N/A	N/A
Baram et al. 2021	SR (Quest)	CD	M±SD	0.7±0.5	N/A	N/A
Karlsson et al. 1992	CA (peanut)	MCD (s)	M±SD	0.50±0.13	N/A	N/A

Massimo et al. 2020	CA (colour gum)	MP	M±SD	3.2±0.4	3.5±0.8	NS
	SR (Quest)	CD	M±SD	1.1±1.0	0.8±0.8	NS
Nakayama et al. 2004	SR (Quest)	CD	Prevalence	28%	6%	**p ≤ 0.05**
Persson et al. 1992	SR (Quest)	CD	Prevalence	33.3%	3.4%	NS
Ribeiro et al. 2017[a]	CA (Optocal cube)	MP (particle size, mm)	M±SD	5.7±0.9	4.2±1.1	**p ≤ 0.01**
	CA (Optocal cube)	MCD (s)	M±SD	0.77±0.16	0.61±0.10	**p ≤ 0.05**
Ribeiro et al. 2017[b]	CA (Optocal cube)	ME (weight loss, %)	M±SD	7.0±9.8%	13.0±11.3%	**p ≤ 0.05**
Ribeiro et al. 2018	CA (Optocal cube)	MP (particle size, mm)	M±SD	5.8±1.1	N/A	N/A
	CA (Optocal cube)	MCD (s)	M±SD	0.61±0.14	N/A	N/A
Van Stiphout et al. 2018	SR (Quest)	CD	Prevalence	29.7%	4.1%	**p ≤ 0.01**
Wooten Watts et al. 1999	SR (Quest)	CD	Prevalence	19%	6%	**p ≤ 0.05**

Unspecified TMD

Article	**Method**	**Outcome measure**		**PD**	**Control**	**p-value**
Bakke et al. 2011	SR+CA (NOT-S)	U-TMD	M±SD	5.5±2.9	0.7±0.0	**p ≤ 0.01**
Baram et al. 2020	SR+CA (NOT-S)	U-TMD	M±SD	3.1±2.0	N/A	N/A
Baram et al. 2021	SR (NOT-S)	U-TMD	M±SD	1.6±1.2	N/A	N/A
Baretto Tavares et al. 2021	SR + CA (RDC/TMD)	U-TMD	Prevalence	61.7%	N/A	N/A
Baumann et al. 2020	SR + CA (Helkimo)	U-TMD	Prevalence	37.1%	2.4%	N/A
Choi et al. 2021	History (ICD-10)	U-TMD	Prevalence	1.0%	0.6%	**p ≤ 0.05**
da Costa Silva et al. 2015	SR + CA (RDC/TMD)	U-TMD	Prevalence	20.3%	N/A	N/A
da Costa Silva et al. 2016	SR + CA (RDC/TMD)	U-TMD	Prevalence	23.8%	N/A	N/A
Massimo et al. 2020	SR+CA (NOT-S)	U-TMD	M±SD	4.5±2.3	1.1±1.1	**p ≤ 0.01**

Non-painful TMD

Article	**Method**	**Outcome measure**		**PD**	**Control**	**p-value**
Persson et al. 1992	SR (Quest)	NP-TMD (Joint function)	Prevalence	40%	50%	NS
Verhoeff et al., 2018	SR (DC/TMD)	NP-TMD (locks)	Prevalence	12.3%	18.3%	NS
Wooten Watts et al. 1999	SR (Quest)	NP-TMD (sounds)	Prevalence	27%	17%	**p ≤ 0.05**

Sensory disturbances						
Article	**Method**	**Outcome measure**		**PD**	**Control**	**p-value**
Bakke et al. 2011	CA	OS (response time, s)	M±SD	8.6±6.5	5.9±3.1	p=0.10
Bakke et al. 2011	CA	OS (identifications)	M±SD	0.6±0.6	0.8±0.2	p=0.20
Bruxism						
Article	**Method**	**Outcome measure**		**PD**	**Control**	**p-value**
Abe et al. 2013	CA (PSG)	Bruxism (SB); RMMA	Episode index	0.52	0.00	**p ≤ 0.01**
	CA (PSG)	Bruxism (SB); RMMA	Burst index	1.94	0.00	**p ≤ 0.01**
Bonenfant et al. 2016	SR (Quest)	Bruxism (?); OHS	Prevalence	4.8%	N/A	N/A
Kwak et al. 2009	CA (Observe)	Bruxism (AB)	Prevalence	2.2%	N/A	N/A
Persson et al. 1992	SR (Quest)	Bruxism (?)	Prevalence	56.7%	2.1%	NS
Verhoeff et al. 2018	SR (DC/TMD)	Bruxism (AB)	Prevalence	46.0%	9.1%	**p ≤ 0.01**
	SR (DC/TMD)	Bruxism (SB)	Prevalence	24.3%	8.3%	**p ≤ 0.01**
Wooten Watts et al. 1999	SR (Quest)	Involuntary jaw movement	Prevalence	16%	0%	**p ≤ 0.05**
	SR (Quest)	Bruxism (?)	Prevalence	30%	21%	NS

Note | *p= p-value,?= unknown, SR= Self-report, CA= Clinical Assessment, M=Mean, SD= standard deviation, %=percentage, Quest= Questionnaire,* exp= experimental, N/A= Not Applicable; NS= Not significant; CC sEMG= Craniovercial Overall surface electromyography; MM= Marginal Mean, MMO= maximum mouth opening; s= seconds; mm= millimeters; cm= centimeter; MVC= Maximum Voluntary Contraction; N= Newton; EMG= Electromyography; MCD= masticatory cycle duration; RMMA= Rhytmic Masticatory Muscle Activity; OHS= Oral Habit Score; AB=Awake Bruxism; SB=Sleep bruxism, observe=observation by caregivers, OS=Oral Stereognosis, U-TMD=Unspecified Temporomandibular Disorder, CD=Chewing Difficulties, ME= Masticatory Efficiency, MP= Masticatory Performance, NOT-S= Nordic Orofacial Test-Screening, RDC/TMD= Research Diagnostic Criteria for Temporomandibular Disorders, DC/TMD = Diagnostic Criteria for Temporomandibular Disorders, ICD-10= 10th edition of the internation statistical classification of Diseases and Related Health Problems, PSG= Polysomnography, ^{1}= within PD patients the ridigity group, ^{2}=within PD patients the tremor group, ^{3}= measured from lip to lip, *=estimation because of reading figure

Table 4. Results of case studies and case series, in PD patients .

Article	Number of cases	Age (in years)	Gender (%Female)	Variable	Outcome
Coon et al. 2012	1	65	100%	BMD	6 Weeks after starting 25/100mg carbidopa/ levodopa BMD started; after discontinuation carbidopa/levodopa the symptoms disappeared in 2 weeks' time. Pramipexol in higher dosages (1.5mg) was prescribed with releave of PD symptoms, but without BMD.
Ford et al. 1996	5	66 (M)	60%	BMD	All cases experienced burning sensation and oral discomfort of the oral cavity, gums and/ or face.
Magee et al. 1970	1	53	100%	Bruxism	After using levodopa for several months, where the dosages was slowly build up to 4.5gram, PD symptoms were acceptable. However, after five months of therapy, bruxism occurred with severe tooth wear as consequence. A cast was made to protect her teeth for further development of tooth wear, but did not adjust or stopped the levodopa therapy.
Minagi et al. 1998	1	71	100%	TMD pain	Experienced frequent and excessive involuntary movement to the right side of the TMJ, with her mandible caused pain at the location of her TMJ. After making an appliance which restricted her movement, the pain diminished after one week.

Note| M=Mean; %=Percentage; PD=Parkinson's Disease; BMD=Burning Mouth Disorder; TMD=Temporomandibular Disorder; TMJ=Temporomandibular Joint; mg=milligram;

Table 5. Results for the possible associated PD-related variables (viz., gender, disease duration, disease severity, and medication usage) with orofacial pain and dysfunction complaints in patients with PD, compared with healthy controls.

Associated factors			
		Gender	
Article	**Males**	**Females**	**p-value**
Bonenfant et al. 2016	10.3% BMD	4.3% BMD	N/A
Clifford et al. 1998	10 BMD	17 BMD	**p ≤ 0.01**
da Costa Silva et al. 2015	41.7% prevalence of unspecified TMD	58.3% prevalence of unspecified TMD	N/A
O'neill et al. 2021	5.9% prevalence orofacial pain	10.4% orofacial pain prevalence	N/A
		Disease duration	
Article	**Variable**		**PD**
Bakke et al. 2011	↓ Unspecified TMD when duration of disease is longer		**p ≤ 0.05**
	↑ Self-reported chewing difficulties when duration of disease is longer		**p ≤ 0.05**
Baram et al. 2021	↓ Unspecified TMD when duration of disease is longer		p=0.5
	Masticatory ability is not associated with duration of the disease		NS
Bonenfant et al. 2016	Median disease duration is equal for BMD and non-BMD group		NS
O'neill et al. 2021	↑ Disease duration when BMD is present (5.8±7.3) than without BMD (2.9±1.9)		**p ≤ 0.05**
		Disease severity	
Article	**Variable**		**PD**
Bakke et al. 2011	↓ Orofacial function when disease severity is worse		**p ≤ 0.01**
	↑ Self-reported chewing difficulties when disease severity is worse		**p ≤ 0.01**
	↑ Sensory disturbances when disease severity is worse		**p ≤ 0.01**
	No association between tenderness of jaw elevator muscles and disease severity		p=0.7
	↑ Sensory disturbances (recognition) when disease severity is worse		**p ≤ 0.05**
	No association between mouth opening and severity of the disease		NS
Baram et al. 2020	↑ Orofacial dysfunction when disease severity is worse		**p ≤ 0.01**
Baram et al. 2021	↓ Orofacial function (NOT-S) when disease severity is worse		**p ≤ 0.01**
	↓ Masticatory ability when disease severity is worse		**p ≤ 0.05**
Bonenfant et al. 2016	↑ Median H&Y scale when BMD is present (3) when compared to no BMD (2.5)		NS
Chen et al. 2019	↑ Incidence of TMD during the first and second year of the disease		**p ≤ 0.05**
da Costa Silva et al. 2015	No association between TMD and disease severity		NS
Massimo et al. 2020	No association between masticatory efficiency (gum chewing) and disease severity		NS
O'Neill et al. 2021	↑ Prevalence of orofacial pain when disease severity (subdomains MDS-UPDRS) is worse		?
Rodriguez-Violante et al. 2017	↑ Prevalence of orofacial pain scores when disease severity is worse		**p ≤ 0.01**
van Stiphout et al. 2018	↑ Chewing and biting difficulties when disease severity is worse		**p ≤ 0.05**

Medication usage		
Article	**Variable**	**PD**
Bonenfant et al. 2016	↓ Mean LEDD score when BMD is present (630.1mg/day) when compared to no BMD (653.9mg/day)	NS
Karlsson et al. 1992	↓ Slower movements and mandibular displacements after ON-phase compared to OFF-period	**$p \leq 0.05$**
O'Neill et al. 2021	↑ Median LEDD score when BMD is present (465mg/day) when compared to no BMD (400mg/day)	**$p \leq 0.01$***
	↑ Median LEDD score when grinding pain is present (462.5mg/day) when compared to no pain (400mg/day)	**$p \leq 0.01$***
Ribeiro et al. 2018 [MF]	↑ Bigger range of jaw motion (lateral deviation, protrusion, laterotrusion) during ON-period compared to OFF-period	**$p \leq 0.01$**
	MMO during ON-period (31.0±5.6 mm) compared to MMO during OFF-period (31.3±3.1 mm)	NS
	↑ Higher maximum bite force during ON-period compared to OFF-period	**$p \leq 0.01$**
	↑ Better masticatory performance ON-period compared to OFF-period	**$p \leq 0.01$**
Robbertson & Hammerstad 1996	↑ MMO during the ON-period compared to the OFF-period	**$p \leq 0.01$**
	↓ EMG pattern during during clenching in the OFF-period compared to ON-period	N/A
Robbertson et al. 2001	↑ Jaw opening velocity and MMO during ON-period compared to OFF-period	N/A
Robbertson et al. 2011	↑ Jaw opening and closing velocity during ON-period compared to OFF-period	N/A

Note| %= percentage, p =p-value, ?= unknown, NS=Not Statistically Different; N/A=Not Applicable; ↑=higher; ↓=lower; BMD=Burning Mouth Disorder; TMD=Temporomandibular Disorder; NOT-S=Nordic Orofacial Test Screening; H&Y=Hoehn & Yahr Scale; MDS-UPDRS=Movement Disorders Society Unified Parkinson Disease Rating Scale; ON= dopaminergic therapy works optimal; OFF=Dopaminergic therapy is working suboptimal; LEDD=Levodopa Equivalent Daily Dosages; mg/day = milligrams per day, MMO=Maximum Mouth Opening; EMG=Electromyography, *=After Bonferroni correction statistical significance dissapeared

Appendix

Appendix 1| session results of search PubMed, Embase.com, Wiley/Cochrane, Web of Science, PubMed Session Results (20 Jan 2022)

Search	Query	Items found
#9	**#7 OR #8**	2,860
#8	**#1 AND #4**	256
#7	**#5 OR #6**	2,661
#6	#1 AND #3	1,617
#5	#1 AND #2	1,270
#4	(("Quality of Life"[Mesh] OR "quality of life"[tiab] OR "life qualit*"[tiab] OR "living qualit*"[tiab] OR "quality of living"[tiab] OR "Activities of Daily Living"[Mesh] OR "activities of daily living"[tiab] OR "activity of daily living"[tiab] OR "activities of daily life"[tiab] OR "activity of daily life"[tiab] OR "daily living activit*"[tiab] OR "daily life activit*"[tiab] OR "adl"[tiab] OR "chronic limitation of activity"[tiab] OR "self care*"[tiab] OR "Health Status"[Mesh] OR "health status"[tiab] OR "level of health"[tiab] OR "health level*"[tiab] OR "qol"[tiab] OR "hrql"[tiab] OR "hrqol"[tiab]) AND (oral[tiab])) OR "OHRQoL"[tiab]	29,820
#3	"Dyskinesias"[Mesh:NoExp] OR "Mastication"[Mesh] OR "Facial Pain"[Mesh] OR "Facial Neuralgia"[Mesh] OR "Musculoskeletal Pain"[Mesh:NoExp] OR "Myalgia"[Mesh] OR "Arthralgia"[Mesh:NoExp] OR "Neuralgia"[Mesh:NoExp] OR "Burning Mouth Syndrome"[Mesh] OR "Craniomandibular Disorders"[Mesh] OR "Bruxism"[Mesh] OR "Dental Occlusion"[Mesh] OR "Malocclusion"[Mesh] OR "Tooth Wear"[Mesh] OR "oral function*"[tiab] OR "oral dyskinesia*"[tiab] OR "orofacial function*"[tiab] OR "orofacial dyskinesia*"[tiab] OR "mastication"[tiab] OR "chewing"[tiab] OR "tooth mobilit*"[tiab] OR "jaw mobilit*"[tiab] OR "mandibular mobilit*"[tiab] OR "tooth movement*"[tiab] OR "jaw movement*"[tiab] OR "mandibular movement*"[tiab] OR "orofacial pain"[tiab] OR "craniofacial pain"[tiab] OR "myofacial pain"[tiab] OR "facial pain"[tiab] OR "neuropathic pain"[tiab] OR "burning mouth"[tiab] OR "craniomandibular disorder*"[tiab] OR "cranio-mandibular disorder*"[tiab] OR "neuralgia"[tiab] OR "trigeminal"[tiab] OR "Tic Douloureux"[tiab] OR "temporomandibular joint dis*"[tiab] OR "temporo-mandibular joint dis*"[tiab] OR "temporomandibular dysfunction*"[tiab] OR "temporo-mandibular dysfunction*"[tiab] OR "temporomandibular disorder*"[tiab] OR "temporo-mandibular disorder*"[tiab] OR "TMJ dis*"[tiab] OR "TMD"[tiab]	192,191
#2	"Oral Health"[Mesh] OR "Mouth Diseases"[Mesh] OR "Tooth Diseases"[Mesh] OR "Periodontal Prosthesis"[Mesh] OR "Periodontal Index"[Mesh] OR "Prosthodontics"[Mesh] OR "oral health"[tiab] OR "oral hygiene"[tiab] OR "dental"[tiab] OR "dentistry"[tiab] OR "mouth"[tiab] OR "tooth"[tiab] OR "teeth"[tiab] OR "jaw"[tiab] OR "jaws"[tiab] OR "periodont*"[tiab] OR "parodont*"[tiab] OR "Pyorrhea Alveolaris"[tiab] OR "periapical"[tiab] OR "gingiva*"[tiab] OR "gingivi*"[tiab] OR (("gum"[tiab] OR "gums"[tiab]) AND ("inflammat*"[tiab] OR "disease*"[tiab])) OR "caries"[tiab] OR "carious"[tiab] OR "edentulous"[tiab] OR "prosthes*"[tiab] OR "prosthetic*"[tiab] OR "prosthodont*"[tiab]	982,386
#1	"Parkinsonian Disorders"[Mesh] OR "parkinson*"[tiab]	143,272

Embase.com Session Results (20 Jan 2022)

Search	Query	Items found
#10	**#9 NOT ('conference abstract'/it OR 'conference review'/it)**	4,695
#9	**#7 OR #8**	6,093
#8	**#1 AND #4**	692
#7	**#5 OR #6**	5,547
#6	#1 AND #3	2,045
#5	#1 AND #2	4,009
#4	(('quality of life'/exp OR 'quality of life':ab,ti,kw OR 'life qualit*':ab,ti,kw OR 'living qualit*':ab,ti,kw OR 'quality of living':ab,ti,kw OR 'daily life activity'/exp OR 'activities of daily living':ab,ti,kw OR 'activity of daily living':ab,ti,kw OR 'activities of daily life':ab,ti,kw OR 'activity of daily life':ab,ti,kw OR 'daily living activit*':ab,ti,kw OR 'daily life activit*':ab,ti,kw OR 'adl':ab,ti,kw OR 'chronic limitation of activity':ab,ti,kw OR 'self care*':ab,ti,kw OR 'health status'/exp OR 'health status':ab,ti,kw OR 'level of health':ab,ti,kw OR 'health level*':ab,ti,kw OR 'qol':ab,ti,kw OR 'hrql':ab,ti,kw OR 'hrqol':ab,ti,kw) AND (oral:ab,ti,kw)) OR 'oral health related quality of life'/exp OR 'OHRQoL':ab,ti,kw	45,365
#3	'mastication'/exp OR 'face pain'/exp OR 'musculoskeletal pain'/de OR 'myofascial pain'/exp OR 'arthralgia'/exp OR 'neuralgia'/de OR 'burning mouth syndrome'/exp OR 'temporomandibular joint disorder'/exp OR 'bruxism'/exp OR 'tooth occlusion'/exp OR 'malocclusion'/exp OR 'jaw movement'/exp OR 'oral function*':ab,ti,kw OR 'oral dyskinesia*':ab,ti,kw OR 'orofacial function*':ab,ti,kw OR 'orofacial dyskinesia*':ab,ti,kw OR 'mastication':ab,ti,kw OR 'chewing':ab,ti,kw OR 'tooth mobilit*':ab,ti,kw OR 'jaw mobilit*':ab,ti,kw OR 'mandibular mobilit*':ab,ti,kw OR 'tooth movement*':ab,ti,kw OR 'jaw movement*':ab,ti,kw OR 'mandibular movement*':ab,ti,kw OR 'orofacial pain':ab,ti,kw OR 'craniofacial pain':ab,ti,kw OR 'myofacial pain':ab,ti,kw OR 'facial pain':ab,ti,kw OR 'neuropathic pain':ab,ti,kw OR 'burning mouth':ab,ti,kw OR 'craniomandibular disorder*':ab,ti,kw OR 'cranio-mandibular disorder*':ab,ti,kw OR neuralgia:ab,ti,kw OR trigeminal:ab,ti,kw OR 'Tic Douloureux':ab,ti,kw OR 'temporomandibular joint dis*':ab,ti,kw OR 'temporo-mandibular joint dis*':ab,ti,kw OR 'temporomandibular dysfunction*':ab,ti,kw OR 'temporo-mandibular dysfunction*':ab,ti,kw OR 'temporomandibular disorder*':ab,ti,kw OR 'temporo-mandibular disorder*':ab,ti,kw OR 'TMJ dis*':ab,ti,kw OR TMD:ab,ti,kw	282,483
#2	'oral health related quality of life'/exp OR 'oral health status'/exp OR 'mouth disease'/exp OR 'periodontic device'/exp OR 'dental disease assessment'/exp OR 'prosthodontics'/exp OR 'oral health':ab,ti,kw OR 'oral hygiene':ab,ti,kw OR dental:ab,ti,kw OR dentistry:ab,ti,kw OR mouth:ab,ti,kw OR tooth:ab,ti,kw OR teeth:ab,ti,kw OR jaw:ab,ti,kw OR jaws:ab,ti,kw OR periodont*:ab,ti,kw OR parodont*:ab,ti,kw OR 'Pyorrhea Alveolaris':ab,ti,kw OR periapical:ab,ti,kw OR gingiva*:ab,ti,kw OR gingivi*:ab,ti,kw OR ((gum OR gums) NEAR/3 (inflammat* OR disease*)):ab,ti,kw OR caries:ab,ti,kw OR carious:ab,ti,kw OR edentulous:ab,ti,kw OR prosthes*:ab,ti,kw OR prosthetic*:ab,ti,kw OR prosthodont*:ab,ti,kw	1,181,125
#1	'Parkinson disease'/exp OR 'parkinsonism'/exp OR parkinson*:ab,ti,kw	232,537

Web of Science (Core Collection) Session Results (20 Jan 2022)

Search	Query	Items found
#9	**#7 OR #8**	2,263
#8	**#1 AND #4**	345
#7	**#5 OR #6**	1,982
#6	#1 AND #3	1,083
#5	#1 AND #2	1,148
#4	TS=(((“quality of life” OR “life qualit*” OR “living qualit*” OR “quality of living” OR “activities of daily living” OR “activity of daily living” OR “activities of daily life” OR “activity of daily life” OR “daily living activit*” OR “daily life activit*” OR “adl” OR “chronic limitation of activity” OR “self care*” OR “health status” OR “level of health” OR “health level*” OR “qol” OR “hrql” OR “hrqol”) AND (oral)) OR “OHRQoL”)	29,779
#3	TS=(“oral function*” OR “oral dyskinesia*” OR “orofacial function*” OR “orofacial dyskinesia*” OR “mastication” OR “chewing” OR “tooth mobilit*” OR “jaw mobilit*” OR “mandibular mobilit*” OR “tooth movement*” OR “jaw movement*” OR “mandibular movement*” OR “orofacial pain” OR “craniofacial pain” OR “myofacial pain” OR “facial pain” OR “neuropathic pain” OR “burning mouth” OR “craniomandibular disorder*” OR “cranio-mandibular disorder*” OR “neuralgia” OR “trigeminal” OR “Tic Douloureux” OR “temporomandibular joint dis*” OR “temporo-mandibular joint dis*” OR “temporomandibular dysfunction*” OR “temporo-mandibular dysfunction*” OR “temporomandibular disorder*” OR “temporo-mandibular disorder*” OR “TMJ dis*” OR “TMD”)	121,778
#2	TS=(“oral health” OR “oral hygiene” OR “dental” OR “dentistry” OR “mouth” OR “tooth” OR “teeth” OR “jaw” OR “jaws” OR “periodont*” OR “parodont*” OR “Pyorrhea Alveolaris” OR “periapical” OR “gingiva*” OR “gingivi*” OR ((“gum” OR “gums”) NEAR/3 (“inflammat*” OR “disease*”)) OR “caries” OR “carious” OR “edentulous” OR “prosthes*” OR “prosthetic*” OR “prosthodont*”)	653,348
#1	TS=(“parkinson*”)	195,491

Wiley / Cochrane Library Session Results (20 Jan 2022)

Search	Query	Items found
#9	**#7 OR #8**	497
#8	**#1 AND #4**	260
#7	**#5 OR #6**	256
#6	#1 AND #3	59
#5	#1 AND #2	208
#4	((((quality NEXT of NEXT life) OR (life NEXT qualit*) OR (living NEXT qualit*) OR (quality NEXT of NEXT living) OR (activities NEXT of NEXT daily NEXT living) OR (activity NEXT of NEXT daily NEXT living) OR (activities NEXT of NEXT daily NEXT life) OR (activity NEXT of NEXT daily NEXT life) OR (daily NEXT living NEXT activit*) OR (daily NEXT life NEXT activit*) OR adl OR (chronic NEXT limitation NEXT of NEXT activity) OR (self NEXT care*) OR (health NEXT status) OR (level NEXT of NEXT health) OR (health NEXT level*) OR qol OR hrql OR hrqol) AND (oral)) OR OHRQoL):ab,ti,kw	15,358
#3	((oral NEXT function*) OR (oral NEXT dyskinesia*) OR (orofacial NEXT function*) OR (orofacial NEXT dyskinesia*) OR mastication OR chewing OR (tooth NEXT mobilit*) OR (jaw NEXT mobilit*) OR (mandibular NEXT mobilit*) OR (tooth NEXT movement*) OR (jaw NEXT movement*) OR (mandibular NEXT movement*) OR (orofacial NEXT pain) OR (craniofacial NEXT pain) OR (myofacial NEXT pain) OR (facial NEXT pain) OR (neuropathic NEXT pain) OR (burning NEXT mouth) OR (craniomandibular NEXT disorder*) OR (cranio-mandibular NEXT disorder*) OR neuralgia OR trigeminal OR (Tic NEXT Douloureux) OR ("temporomandibular joint" NEXT dis*) OR ("temporo-mandibular joint" NEXT dis*) OR (temporomandibular NEXT dysfunction*) OR (temporo-mandibular NEXT dysfunction*) OR (temporomandibular NEXT disorder*) OR (temporo-mandibular NEXT disorder*) OR (TMJ NEXT dis*) OR TMD):ab,ti,kw	12,875
#2	((oral NEXT health) OR (oral NEXT hygiene) OR dental OR dentistry OR mouth OR tooth OR teeth OR jaw OR jaws OR periodont* OR parodont* OR (Pyorrhea NEXT Alveolaris) OR periapical OR gingiva* OR gingivi* OR ((gum OR gums) NEAR/3 (inflammat* OR disease*)) OR caries OR carious OR edentulous OR prosthes* OR prosthetic* OR prosthodont*):ab,ti,kw	77,022
#1	parkinson*:ab,ti,kw	11,806

Chapter 7

Parkinson's disease, temporomandibular disorders and bruxism: a pilot study

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Abstract

Background: even though bruxism and Parkinson's disease (PD) share common characte-ristics, their relation is still not clear. Both bruxism and PD are movement disorders. In addition, patients with bruxism as well as those with PD complain about musculoskeletal pain, including temporomandibular disorders (TMD) pain.

Objectives: therefore, the aim of this pilot study was to gain more insight into the possible relation between bruxism and TMD on the one hand and PD on the other.

Methods: in total, 801 persons gave their written informed consent and agreed to participate in the study filling in a questionnaire. Complete data were collected from 708 persons (368 with PD or Parkinsonism (PR) and 340 controls) and were included in the analysis. The questionnaire included the graded chronic pain scale, the DC/TMD oral behaviour checklist, the DC/TMD symptom questionnaire, and the TMD pain screener. In addition, a question about self-reported tooth wear was included. The chi-square test and independent samples t-test were used for the data analysis.

Results: patients with PD/PR reported significantly more often bruxism during sleep and wakefulness than controls. Also, patients with PD/PR had more often possible TMD and reported a significantly higher mean pain intensity in the orofacial region than controls. There was no significant difference in complaints of jaw locking between the patient group and the control group. A tendency towards a significant association was found between PD/PR and tooth wear.

Conclusion: there is a relation between PD/PR and bruxism. Furthermore, a relation of PD/PR with TMD pain is suggested to be present.

Keywords: Parkinson disease, bruxism, facial pain, pilot project, questionnaire, temporo-mandibular joint disorders

Introduction

In the near future, human's life expectancy is estimated to increase significantly: in 1950 only eight percent of the population was above 65 years old, while in 2040 this prevalence is estimated to become triple reaching almost 26%[1]. Additionally, in the Netherlands, the actual number of inhabitants is also expected to increase with more than 7.5% amongst others because of the improvement of the health care system[1]. This estimated aging of the population is expected to cause an increase of the prevalence of age-related diseases like the neurodegenerative diseases. Neurodegenerative diseases, such as Alzheimer's, Huntington's, and Parkinson's disease (PD), affect neurons in the central nervous system and especially in the brain. Currently, there is no treatment to cure them and therefore they can progress in the long term, causing movement disorders and problems affecting the patients' mental state[2].

PD is a movement disorder that causes serious impairment in patients' life. The prevalence of PD in 2007 in the Netherlands was estimated between 201-372 per 100.000 persons. Statistics Netherlands (CBS) predicts an increase in the prevalence of about 40% in 2025[2]. Even though the exact pathophysiological mechanism of PD is not fully understood, it is considered to be caused by a deficiency in the dopamine levels due to degeneration of neurons in the substantia nigra. In PD, as a result of the reduced dopamine levels in the striatum, fluent movements of the human body are disturbed[3]. The same symptoms as PD can also be present in patients suffering from other diseases in which the dopamine producing cells are affected. These patients are considered to suffer from Parkinsonism (PR), which is a general term that reflects the characteristic symptoms of PD.

Until now, the prevalence of oromandibular movement disorders in patients with PD/PR is not yet studied. One of the most common oromandibular movement disorders in humans is bruxism. Bruxism is defined as a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible and has two distinct circadian manifestations: it can occur during sleep (indicated as sleep bruxism) or during wakefulness (indicated as awake bruxism)[4]. Its prevalence in adults can vary between 8% and 31.4%, depending on factors like the methodology and the population studied[5]. Bruxism is considered one of the important risk factors for the initiation and perpetuation of temporomandibular disorders (TMD)[6].

TMD is a collective term embracing disorders of the masticatory muscles, the temporomandibular joint, and adjacent structures[7]. Painful TMD is considered the second most common cause of orofacial pain after dental pain[8]. The prevalence of painful TMD is about 10% in adults[9]. Other symptoms of TMD include limitations in the movement of the mandible (either while opening or during closing of the mouth), joint sounds, and headache attributed to TMD[10]. In the aetiology of TMD, oral parafunctions like bruxism are considered to play an important role[6].

Although the possible relation between bruxism and PD has not been studied yet, some suggestions for the existence of such relationship can be derived from the literature as mentioned earlier, PD and bruxism are both movement disorders. Moreover, bruxism is considered to be regulated centrally and not peripherally, with an important role of the dopaminergic nervous network of the brain[11]. PD is also a disease related to a shortage of dopamine. This can cause uncontrolled movements in the orofacial region as well[3]. Furthermore, specific antidepressants (like Selective Serotonin Reuptake Inhibitors; SSRI's), which have bruxism as a possible side effect, work through inhibition of specific dopaminergic neurons. Because of the reduction of dopamine, the possibility of developing uncontrolled movements like bruxism increases[12]. In addition, in about 9% of the cases, depression already exists in PD patients before the actual diagnosis of PD is established[2]. Stress and depressed feelings are also risk factors for awake bruxism[6]. Furthermore, a case report showed a patient with a basal ganglia infarct who developed bruxism. This report concluded that there could be a connection between bruxism and a dysfunction of the dopaminergic pathway[13].

Even less information is available about the possible relation between PD and TMD. A possible link is that besides restrictions in movements, also sensory aspects play a role in both PD as TMD. PD is characterized by the regular presence of pain[14]. The prevalence of pain as a symptom of PD is approximately 30-50%. In 45-74% of these cases, the pain was classified as musculoskeletal pain[15]. Bruxism itself is not painful, but it can be an important risk factor for developing TMD-pain complaints. It is also known that in TMD, orofacial pain is one of the cardinal symptoms. Besides, pain elsewhere in the body is a risk factor for having orofacial pain[16]. Finally, in another study a significantly reduced D1/D2 ratio and an increased amount of D2 receptors was found in patients with atypical facial pain, which suggests that alterations in the striatal dopaminergic system could influence chronic orofacial pain conditions[17].

As mentioned above, little is known so far about a possible relation between PD on the one hand and bruxism and TMD on the other. Although some theories currently exist in the literature, no definite conclusion has been drawn and a causal relationship has not been proven. Within these premises, the aim of the present pilot study was to gain more insight into a possible relation between bruxism and TMD on one hand and PD/PR on the other.

Methods

Patients with a diagnosis of PD or PR were asked to participate in the study (patient group). Patients suffering from other movement disorders than PD or PR were excluded. Partners, caregivers, friends, and non-related persons with a maximum of five years of age difference were asked also to participate (control group). Relatives of the patients and persons with more than five years of age difference were excluded from the control group. Written informed consent was obtained from each participant. The study was independently reviewed and approved by the Medical Ethics Committee of the VU Medical Centre, Amsterdam, The Netherlands (file no. 2015.461; approval date November 26th, 2015).

Questionnaire

Data were collected with the use of a questionnaire (*appendix 1*) that was composed by the authors with questions taken from already existing instruments (appendix 1). There are eighteen questions: about demographics (gender and age; two questions), research location (one question), diagnosis of PD/PR and the possible use of medication (three questions), and bruxism and related problems like TMD/orofacial pain and presence of tooth wear (twelve questions). Except for the question about tooth wear, which was taken from the intake questionnaire of the Clinic of Orofacial Pain and Dysfunction of ACTA, the latter questions were selected from the graded chronic pain scale[18], the DC/TMD oral behaviour checklist[19,20], the DC/TMD symptom questionnaire[10], and the TMD-pain screener[21]. When the participants answered positive to the question 7 (Appendix 1), they were considered having "Orofacial Pain". When the score of the TMD-pain screener was equal or above four, participants were considered having "Possible TMD-pain". Moreover, characteristic pain intensity (CPI) was calculated based on the analysis of the data of the graded chronic pain scale. When a person reported clenching, grinding, or bracing the mandible during sleep or awakening at least "1-3 nights a month" or "Some of the time", this was interpreted as presence of sleep or awake bruxism[4,22].

Data collection

The data were collected from February 8th, 2016, until February 8th, 2017 through visiting unofficial gatherings of PD/PR patients organized by the Dutch Association of PD patients (Parkinson cafés), hospitals, or individual nurses. In addition, advertisement took place through social media, viz., through Facebook and on the website of the Dutch association of PD patients. The advertisement was placed on March 1st, 2016. In order to obtain the same amount of responses regarding the control group, people from several public places, like Schiphol Airport, were also asked to fill in the questionnaire.

Data analysis and statistics

Descriptive data were calculated for all variables. Subsequently, Chi-square test was used to test possible association between the presence of PD/PR and the following variables: orofacial pain, possible TMD-pain, possible sleep or awake bruxism, jaw locking, and tooth wear. Differences between the patient group and the control group were tested with independent sample t-test for the CPI. Statistical analyses were performed with IBM SPSS statistics, version 24. The level of significance was set at $\alpha<0.05$.

Results

801 questionnaires were filled in. Data from 93 persons were excluded from the analysis, because the questionnaires were either not completed (*n* = 69) or contained missing values (*n* = 24) (Figure 1). The demographics and distribution of the patient and control group are shown in Table 1. No significant difference between the excluded and included group on the basis of gender and diagnosis. A significant association between PD/PR and orofacial pain (Table 2) was found. PD/PR patients reported pain more frequently than the control group. Further detailed analysis among the patients who reported orofacial pain (*N* = 178) showed a significant association between PD/PR and possible TMD-pain (Table 2). Regarding the pain intensity (CPI), significantly higher values were found for the patient group in comparison with the control group (Table 3). A significant association was also found between PD/PR and bruxism and at the same time for possible sleep bruxism and possible wake bruxism separately (Table 2).

No association between jaw locking and PD/PR was present (Table 2). Finally, a tendency towards a significant association between PD/PR and tooth wear was found (Table 2). Patients with PD/PR reported significantly more often 'much tooth wear' compared to the control group (Table 4).

Discussion

The aim of this pilot study was to gain more insight into a possible relation between bruxism and orofacial pain or TMD-pain on the one hand and PD/PR on the other. The results showed a significant relation between possible sleep bruxism and PD/PR, and also between possible awake bruxism and PD/PR. Moreover, a significant association was found between orofacial pain, possible TMD-pain, and PD/PR.

In general, establishing the diagnosis of PD is a difficult procedure. Only post-mortem examination can provide 100% certainty. In this study, the clinical diagnosis of PD/PR was used, as it was set by the specialized medical practitioner and was self-reported by the patients. The specificity and sensitivity of the diagnostic accuracy of PD from a general neurologist is 57.8% and 89.2%, respectively[23]. It was not realistic to follow all patients over time in order to confirm the diagnosis through post-mortem examination. There is therefore a slight possibility that people were included in the patient group in whom this diagnosis would not be verified after death. In addition, a number of researchers have reported that there is a preclinical phase of PD in which a diagnosis cannot yet be made, and that PD has several different stages during the progression of the disease[24]. A classification for this progression is described in the literature[25]. Consequently, this would mean that in the control group some people could have had one of the preliminary PD stadia that could not be easily diagnosed. Regardless of this possibility, significant associations with bruxism and TMD-pain were found for the PD/PR group. In future research, it would possibly be more accurate to collaborate directly with a neurologist in order to analyse in which stage the patient is, and if bruxism is associated with PD at specific stages.

In this pilot study, a questionnaire was used for the data collection. This questionnaire was distributed mainly in Parkinson Cafés. Therefore, not the researchers themselves but the individuals organizing the meetings were responsible for introducing the research to the participants, thereby potentially introducing bias or confounders. Moreover, nine of the Parkinson Cafés did not respond and ten Parkinson Cafés did not want to cooperate, which may have reduced the generalizability of the findings of this study. In addition, the questionnaire was designed in a way to gather as much information as possible with the least possible burden for the participants. Nevertheless, some patients experienced difficulties to complete the questionnaire: 69 people did not fill in the questionnaire at all, 19 of whom filled only the first 2 questions and 15 of whom stopped at the question about medication. These missing data may also have led to a reduction of the generalizability of the present findings.

Unfortunately, there was no question about dentures in the questionnaire. Many patients pointed out that they were wearing a denture. This information could have had an influence on the answers to the question about tooth wear. Most people do not know that also dentures can show wear, and that bruxism is also possible in the absence of teeth. Therefore, it is possible that the answers underestimated the presence of bruxism and wear in the group of people with dentures.

The authors expected that people with PD had higher amounts of tooth wear than the control subjects. In practice, the validity of the self-reported question about wear is a matter of debate. This could possibly explain that only a tendency towards a significant association could be found between PD/PR and tooth wear. In further research, it is therefore more valuable to examine patients with the use of the dental wear screener[26] in order to have clinical data regarding tooth wear.

In an experimental model in monkeys, an association was found between PD and jaw movements[27]. The reported changes in range, velocity, and pattern of jaw movements were confirmed in another study[28]. Because of the study design of the present research, only information about jaw locking was present; not about other deviant jaw movements. For future research, the authors suggest to use this determinant as well. Finally, bruxism and TMD was only based on self-report data. Although there is a possibility that TMD is related to bruxism, the relation between both conditions is not linear[6]. It is therefore not possible to assume a direct relation between bruxism, TMD, and PD/PR.

An earlier study[29] reported a higher prevalence of bruxism in patients with PD, but no significant difference with a control group was observed. Furthermore, another study[30] concluded that awake bruxism is rare, but when it is present the association with neurological diseases is more frequently made. In the present study, we did find a relation between possible sleep and awake bruxism and the diagnosis of PD/PR. These results are in agreement with the study of Tae Kwak et al. (2009)[30]. Also, in the present study, we did find a higher prevalence of bruxism in patients with PD. However, we did find a significant relation between the two groups. This can be due to the large power of our study.

In the current literature, there were also some contradictions present. The highest prevalence of bruxism is described around the age of 45 years[5]. In the present study though, the average age was much higher, viz., 67 years. It is therefore possible that because of the retrospective design of this study, people did not remember experiencing bruxism-related problems before. Therefore, it could be true that patients and controls noted less parafunctions and pain than they actually suffered from. However, this effect most likely occurs equally in controls and patients with PD/PR. Moreover, earlier studies described that a short-term use of L-dopa can result in a reduction of sleep bruxism[31]. Although the effect of the long-term use of L-dopa is not yet clear, the researchers suggested that there may be a relation between the increase of bruxism a long-term use of L-dopa. A case study describing a patient who developed bruxism as a result of levodopa therapy supports these suggestions[32]. In this study, there is the possibility that because 99.4% of the people with PD/PR used levodopa, with or without combination therapy, the results could be influenced. Also, a side effect from dopaminergic medication is dyskinesia (a condition that is, amongst others, characterized by choreatic movements) and it is therefore possible that if present in the orofacial region, dyskinesia was identified as possible bruxism. Because the population in this study was not always very accurate at filling in the questions about medication, it was not possible to verify these results and to assess if the use of levodopa or other dopaminergic medication influenced the bruxism behaviour. Additional clinical research with more objective lists of medication would increase our insight in this possible association. Finally, another study concluded that self-reported bruxism has a low sensitivity (62%) and specificity (50.8%)[33] because of the fact that people are often not aware of their behaviour. Also clenching does not produce sounds and report of muscle fatigue at awakening is not a good indicator for sleep bruxism. This could explain why only few people reported sleep bruxism.

Regarding pain intensity, a number of studies, mainly in animals, have reported higher values in PD patients[15,34]. In the present study, a relation was found between the characteristic pain intensity of orofacial pain and PD/PR, where patients with PD/PR noted a higher mean of pain intensity than the control group. In the literature, no clear relation was found between oral parafunctions like bruxism and orofacial pain. In this study, a significant difference in the mean value of pain intensity was found: people who did not report bruxism behaviour had a significantly lower mean in pain intensity than people who reported bruxism behaviour, which is in accordance with other reports[20].

Clinical history, physical examination, and the reaction to medication is nowadays still the main approach in order to set the diagnosis of PD. With biomarkers and Magnetic Resonance Imaging (MRI), it is possible to distinguish between PD and other neurodegenerative diseases. However, it is still not possible to see whether PD is the correct diagnosis with these additional tests. When a relation with PD and bruxism is proven, bruxism could be of diagnostic value. The main reason is that dentists see their patients more frequently than the General medical practitioner (GP). So, it is possible that an earlier referral from the dentist to the GP or neurologist could be made.

For future research, a more clinical approach is recommended, where a practitioner could examine patients for a more definite diagnosis of bruxism, TMD, or for example if factors like tooth wear are present. Specifically, a diagnosis according to the Diagnostic Criteria for Temporomandibular Disorders[10] would yield more possibilities to compare different research projects at an international level. Also, collaboration with a specialised neurologist is an advantage to determine the progression of the disease and the medication used. Finally, a longitudinal study would be suggested in order to give a definite answer to the question whether in selected cases, bruxism and Parkinson's disease have a causal relation. Eventually, our goal is to see whether bruxism could be a prodrome for developing Parkinson's disease.

Conclusions

The current findings suggest that there is a relation between Parkinson's disease/Parkinsonism and bruxism behaviour. Furthermore, in the population studied, a relation of PD/PR and TMD-pain is also present.

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Disclosure: The study protocol was reviewed from the medical ethics committee of the Free University Medical Centre (Vrij Universiteit Medisch Centrum-VUmc) and was considered not being covered by the Act Medical Scientific Research in Humans according to the Dutch legislation for medical research in humans (Wet medisch-wetenschapelijk onderzoek-WMO). This decision was made because of the cross-sectional study design and the use of the short questionnaire. As such, the study protocol was accepted by the medical ethics committee of the VUmc, who gave a non-WMO approval-statement (file no. 2015.461, approval date November 26th, 2015). An extra permission was given for an amendment (file no. A2016.459, approval date December 14th, 2016), in order to further expand our control group with participants recruited in public locations.

Conflict of interest statement: The authors declare no conflicts of interest.

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Tables

Table 1. Descriptive statistics of all included participants (PD/PR and control group).

Total Participants (N=708)			Controls (N=340)		
Mean ± SD age (years)		67 ± 9.25	Mean ± SD age (years)		65 ± 9.25
Gender	Men	344 (49%)	Diagnosis	No PD/PR	330 (97%)
	Woman	364 (51%)		Unknown	10 (3%)
Questionnaire	Paper	526 (26%)	Gender	Men	125 (37%)
	Internet	182 (74%)		Women	215 (63%)
Data source	Parkinson Café	420 (59%)	**Patients (N=340)**		
	Regional hospital	12 (2%)	Mean ± SD age (years)		68 ± 8.54
	The Dutch association of PD patients	65 (9%)	Diagnosis	PD	352 (96%)
	Social Media	21 (3%)		PR	16 (4%)
	Otherwise	190 (27%)	Gender	Men Woman	219 (60%) 149 (40%)

Table 2. Statistical Results of the Chi-square tests (level of significance: p<0.005).

	Parkinson's disease (PD)/Parkinsonism (PR)	
	X^2	P-value
Orofacial pain	6.304	0.012
TMD pain	17.988	<0.001
Sleep bruxism	10.296	0.001
Awake bruxism	14.864	<0.001
Jaw locking	0.544	0.461
Tooth wear	14.864	0.056

Table 3. Statistical results regarding the characteristic pain intensity (CPI) (independent sample t-test; level of significance: p<0.005)

	Characteristic pain intensity		
	Mean	SD	SE
Controls	35.51	53.40	6.43
PD/PR	80.00	76.32	7.59
	t(167.89)=-4.472, p<0.001		

Table 4. Statistical results regarding tooth wear (adjusted residuals) (chi-square test; level of significance: p<0.005)

	Tooth wear (adjusted residuals)						
	Not	**little**	**some**	**much**	**a lot**	**don't know**	**total**
No (controls)	162	98	29	8	9	34	340
Adjusted residuals	0,5	1,5	1	-2,2	-1	-1,6	
Yes (PD/PR)	169	88	24	21	15	51	368
Adjusted residuals	-0,5	-1,5	-1	2,2	1	1,6	
Total	331	186	53	29	24	85	708

Chapter 3

Is dopaminergic medication dose associated with self-reported bruxism in Parkinson's disease? A cross-sectional, questionnaire-based study

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Abstract

Objectives: it is not clear whether dopaminergic medication influences bruxism behaviour in patients with Parkinson's Disease (PD). Therefore, the aims are to investigate (i) the prevalence of possible (i.e., self-reported) bruxism (sleep and awake) in PD patients, and (ii) whether the use of dopaminergic medication and other factors (viz., demographic characteristics, PD-related factors, and possible consequences of bruxism) are associated with possible bruxism (sleep or awake).

Materials and Methods: this study concerns a secondary analysis of an earlier published study. 395 PD patients (67.9 ± 8.6 years of age; 58.7% males) were included. The Levodopa Equivalent Daily Dosage (LEDD) was used as a measure of the dopaminergic medication level. Subsequently, a logistic regression analysis was performed for the dependent variables 'awake bruxism' and 'sleep bruxism', with the following predictors: gender, age, LEDD, time since PD diagnosis, temporomandibular disorder (TMD) pain, jaw locks, and tooth wear.

Results: the prevalence of possible awake and sleep bruxism was 46.0% and 24.3%, respectively. Awake bruxism was associated with sleep bruxism (OR=8.52; 95% CI 3.56-20.40), TMD pain (OR=4.51; 95% CI 2.31-8.79), and tooth wear (OR=1.87; 95% CI 1.02-3.43). Sleep bruxism was associated with tooth wear (OR=12.49; 95% CI 4.97-31.38) and awake bruxism (OR=9.48; 95% CI 4.24-21.19). Dopaminergic medication dose, was not associated with awake bruxism (OR=1.0; 95% CI 0.99-1.00) or sleep bruxism (OR=1.0; 95% CI 0.99-1.00).

Conclusion: bruxism is a common condition in PD patients, but is not associated with the dopaminergic medication dose.

Clinical Relevance: (oral) health care providers should be alerted about the possibility of sleep and awake bruxism activity in PD patients, along with this activity's possible negative health outcomes (viz., TMD pain, tooth wear).

Keywords: Awake bruxism, dopaminergic medication, levodopa, Parkinson's disease, sleep bruxism, temporomandibular disorders, tooth wear

Introduction

Parkinson's Disease (PD) is a neurodegenerative disease that is characterized by a combination of motor and non-motor symptoms[1]. The classical motor symptoms are bradykinesia, rigidity, and tremor. Examples of non-motor symptoms are cognitive decline, pain, and sleep problems. The etiology of PD is not fully understood, although it is known that degeneration of dopaminergic neurons in the substantia nigra causes deficits in dopamine levels[1]. The prevalence of PD in The Netherlands is registered at 2 per 1000 persons and is expected to rise[2,3]. A cure is not yet available. However, suppression of the symptoms through the administration of dopaminergic replacement therapy is possible. Levodopa, the precursor of dopamine, is commonly used for the medical management of PD symptoms[3].

Bruxism is a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible. It can occur during sleep (i.e., sleep bruxism) or during wakefulness (i.e., awake bruxism)[4]. The prevalence in the Dutch population is estimated, by means of self-report, at 16.5% and 5% for sleep bruxism and awake bruxism, respectively[5]. The etiology of bruxism is multifactorial (viz., biological, psychological, and exogenous factors)[6], and treatment is only necessary when negative health outcomes occur[7]. Because diagnosing bruxism behavior is hard and time-consuming, concensus was reached in which the probability that the behavior is actually present is graded based on the applied assessment tools. In the present study, self-report was used and therefore, a "possible" bruxism diagnosis can be established[4].

In patients with bruxism, a side-to-side (right and left hemisphere) imbalance in the dopaminergic system plays a role, especially of the striatal D2 binding potential[8]. When dopaminergic medication is used, this side-to-side imbalance could be reversed in part or completely. Consequently, the number of bruxism episodes is expected to decrease by using levodopa[9]. The relation between medication usage and bruxism in otherwise healthy individuals has been studied before[10,11]. However, the results of studies on the effect of dopaminergic medication on bruxism are contradictory, some reporting decreases[9,12,13], others increases[14], and yet others no effect[11,15,16].

Whether bruxism activity in PD is caused by the underlying disease process or the use of dopaminergic medication remains unclear. However, it is clear that both bruxism and PD have their origin in the central nervous system and are both influenced by the dopaminergic nigrostriatal system. Therefore, in PD patients, a possible association between awake bruxism/sleep bruxism and dopaminergic medication can be hypothesized[17]. Based on this premise, the aims of this study are (1) to investigate the prevalence of possible (i.e., self-reported) sleep and awake bruxism in a population of PD patients, and (2) determine whether possible sleep or awake bruxism is associated with the use of dopaminergic medication and/or other factors (viz., demographic characteristics, PD-related factors, and possible consequences of bruxism).

Material & Methods

This study concerns a secondary analysis of a published pilot study of Verhoeff et al[17], where the assocation between PD on the one hand, and self-reported bruxism and temporomandibular disorders-pain (TMD-pain) on the other hand, was analyzed[17].

Data Collection

In short, from February 8th, 2016, until February 8th, 2017, data was collected through a questionnaire. People with and without PD were asked to participate in the study. Questionnaires were distributed at unofficial gatherings of the Dutch Association of PD patients (Parkinson Cafés) and social media (viz., Facebook and the website of the Dutch association of PD patients). Only participants with PD were included in the current secondary data analysis. In total, 395 participants with PD filled out the questionnaire.

Dependent variables

To detect possible (i.e., self-reported) awake and sleep bruxism, the Oral Behaviours Checklist (OBC) was used[18]:

- Possible awake bruxism: "*do you clench your teeth during waking hours?*", *"do you press, touch, or hold your teeth together other than while eating (that is, contact between upper and lower teeth)?",* and *"do you hold, tighten, or tense muscles without clenching or bringing teeth together?"* (responses on a 5-point likert scale: "none of the time" is scored as 0, "all of the time" is scored as 4). When participants answered more than or equal to "sometimes (score 2)", possible awake bruxism was recorded as being present.
- Possible sleep bruxism: "*do you clench or grind your teeth when asleep, based on any information you may have?* " (response on a 5-point likert scale: "none of the time" is scored as 0, "4-7 nights/week" is scored as 4). When participants answered more than or equal to "1-3 nights/month (score 2)", possible sleep bruxism was recorded as being present.

Independent variables

Patients were asked to fill in demographic details, general questions about PD, and possible consequences of bruxism (viz., presence of TMD pain, jaw locks, and tooth wear).

- Demographics: "*what is your gender?*" (male/female) and "*what is your age?*" (in years).
- Time since PD diagnosis: *"how long ago where you diagnosed with PD?"* (in years).
- Dopaminergic medication: "*what medication do you use? Please, fill in the type and dosage per day."* (mg/day).
- TMD pain: "*have you ever had pain in your jaw, temple, in the ear, or in front of the ear on either side?"* (yes/no)[19].
- Jaw Locks: *"have you ever had your jaw lock or catch, even for a moment, so that it would not open all the way?"* (yes/no)[19].

- Tooth Wear: *"do you have tooth wear?"* (response on a 5-point likert scale: "no tooth wear" is scored as 0, "much tooth wear" is scored as 4)[20]. A binary outcome is made wherein a score ≥1 was scored as the presence of subjective tooth wear.

Data analysis

Aggregation of medication usage per participant was achieved through the use of the Levodopa Equivalent Daily Dosage (LEDD)[21,22]. According to Tomlinson, the LEDD is a "summation of the calculated conversion factors of each individual antiparkinsonian drug, aligned to 100mg immediate release levodopa"[21](see Table 1 for an example). All LEDD scores were calculated by two independent examiners (NB, MH). When no consensus was reached between the two examiners (N=169), a third examiner (MV) calculated the LEDD separately. When consensus was reached, this LEDD score was used. When no consensus was reached or doubt occurred between the three examiners, a neurologist experienced with calculating LEDD scores was contacted (KvD) (N=35). Most of the time, a conflict occurred because participants did not report that a medicine with slow release was used in stead of immediate release. However, based on the dosage and frequency of the intake it could be determined if immediate release or slow release was taken. Also, handwriting mistakes were made (e.g., 2,75mg instead of 275mg a day). The following general agreement was made: when medication usage was ambiguous or the medication list was not completed, participants were excluded from the data analysis (N=166). Imputation methods were not used because of the amount of missings (>20%) and the non-random distribution of the missings, which is in line with the recommendations when to use imputation methods[23].

Descriptives were calculated for gender, age, time since PD diagnosis, and LEDD. Besides, the prevalence was calculated for awake bruxism and sleep bruxism. Additionally, for the dependent variables awake bruxism and sleep bruxism, multiple logistic regression models were built and odds ratios with confidence intervals were calculated. First, the unadjusted associations with gender, age, time since PD diagnosis, LEDD, TMD pain, jaw locks, and self-reported tooth wear were determined. Variables that showed at least a weak association ($p<0.10$) with the outcome variables 'awake bruxism' or 'sleep bruxism', were included in the multiple logistic regression models. Through the step-by-step approach, the individual variables with the weakest association with the dependent variable were removed from the model (P-to-exit value), until all independent variables showed at least a P-value <0.05 in the final model. OR's smaller than 1.5 and OR's above 5 were considered as small and large clinical effect sizes, respectively24. All analyses were performed using the IBM SPSS Statistics 26 software package (IBM Corp, Armonk, NY, USA). Probability levels of less than 0.05 were considered statistically significant.

Results

In Table 2, the demographic characteristics of the participants are presented. The prevalences of possible awake bruxism and sleep bruxism in patients with PD were 46.0% and 24.3%, respectively (see Table 2).

In this study, the LEDD appeared not to be associated with awake or sleep bruxism (see Tables 3, 4). The results of the single and multiple logistic regression analyses for possible awake bruxism and sleep bruxism are shown in Tables 3 and 4, respectively. The unadjusted associations for awake bruxism showed a possible association ($p<0.10$) with age (odds ratio (OR) 0.94; 95% C.I. 0.92-0.97), sleep bruxism (OR 11.50; 95% C.I. 6.02-21.99), TMD pain (OR 6.78; 95% C.I. 3.97-11.58), jaw locks (OR 3.83; 95% C.I. 1.91-7.71), and tooth wear (OR 4.98; 95% C.I. 3.03-8.17). In the multiple regression analysis, only sleep bruxism (OR 8.82; 95% C.I. 3.56-20.40), TMD pain (OR 4.51; 95% C.I. 2.31-8.79), and tooth wear (OR 1.87; 95% C.I. 1.02-3.43) remained significant. The unadjusted associations for sleep bruxism showed a possible association ($p<0.10$) with female gender (OR 2.24; 95% C.I. 1.36-3.68), age (OR 0.94; 95% C.I. 0.91-0.96), awake bruxism (OR 11.50; 95% C.I. 6.02-21.99), TMD pain (OR 4.65; 95% C.I. 2.74-7.88), jaw locks (OR 3.81; 95% C.I. 1.96-7.41) and tooth wear (OR 16.64; 95% C.I. 7.26-38.13). According to the multiple regression model, the following variables were significantly associated with the report of sleep bruxism: awake bruxism (OR 9.48; 95% C.I. 4.24-21.19) and tooth wear (OR 12.49; 95% C.I. 4.97-31.38). Besides, a trend towards a significant association of sleep bruxism with TMD pain was shown (p-to-exit-value 0.057). For both awake and sleep bruxism models, no statistically significant difference was found between the observed and predicted probabilities, according to the Hosmer and Lemeshow test ($p=0.92$ and 0.85, respectively), concluding that both of the models fit the observed data.

Discussion

The first aim of the present study was to determine the prevalence of possible awake bruxism and sleep bruxism in a population of PD patients. The results showed a respective prevalence of 46.0% and 24.3% for these conditions. The second aim was to investigate possible associations between the dose of dopaminergic medication and the presence of awake and sleep bruxism. The results showed that in a PD population, the Levodopa Equivalent Daily Dosage (LEDD) was not associated with the self-reports of awake and sleep bruxism. Hence, the hypothesis formulated in the introduction, viz., that there is an association between awake bruxism/sleep bruxism and dopaminergic medication, could not be accepted. Furthermore, this study examined whether other factors were significantly associated with self-reported awake and sleep bruxism. Co-occurrence of both awake bruxism and sleep bruxism was observed. Besides, there was an association with tooth wear and both circadian manifestations of bruxism. Finally, awake bruxism was also found to be associated with TMD pain.

Prevalence of awake and sleep bruxism

In the studied population, awake bruxism and sleep bruxism were reported much more often (46% and 24.3%, respectively) than in the general population of the same age (3% and 8.3%, respectively)[5]. While this suggests a large discrepancy with the results of our study, as earlier stated in the hypothesis, it is not that surprising. It is known that populations with neurological conditions show a higher prevalence of awake bruxism[25]. Moreover, some risk factors for bruxism are more prevalent in patients with PD26. Examples of risk factors for bruxism are, amongst others, the presence of stress and depressive thoughts[27-30] and the use of specific types of medication, such as selective

serotonin reuptake inhibitors (SSRI)[10,11]. All of these risk factors are more prevalent in patients with PD than in the general population[26]. Finally, it has been demonstrated that patients with PD have an increased prevalence of sleep problems, resulting in an increased occurrence of arousals from sleep which is in turn related to higher numbers of sleep bruxism events[31,32].

Bruxism and dopaminergic medication

The present study is the first to analyze the association between dopaminergic medication dose and bruxism using LEDD scores in a PD population. As indicated in the Introduction, dopaminergic medication can have variable effects on bruxism in otherwise healthy individuals[9,12-16]. In the present study, however, PD patients were included, which makes it difficult, if not impossible, to compare the present findings to the previously reported ones[9,12-16]. Only in the case report described by Magee (1970)[14], levodopa usage in a PD patient was reported. In that patient, use of levodopa resulted in the occurrence of bruxism behaviour[14]. However, case reports do not provide solid scientific evidence for the described observations. Consequently, the present findings cannot be compared to the study of Magee (1970) either[14]. In sleep laboratory studies, it was shown in healthy volunteers that levodopa exerts an attenuating effect on sleep bruxism[9]. For the usage of bromocriptine, a dopamine agonist, conflicting results were shown. On the one, hand Lobbezoo et al. showed a reduction of sleep bruxism[12], while on the other hand, Lavigne et al. showed that bromocriptine did not reduce or exacerbate sleep bruxism[15]. Finally, Cahlin et al. found that pramipexol, also a dopamine agonist, had no attenuating effect on sleep bruxism[16]. Future studies should be performed in PD patients in whom definite diagnoses of bruxism have been established, as opposed to the possible diagnoses set in the present study. Such studies could also shed further light on the question whether bruxism in PD patients is medication-dependent or rather associated with the neurodegenerative disease itself.

Pharmacokinetics could have played a role in the present results. Dopaminergic medication can act on different types of dopamine receptors. These receptors can have decreasing or increasing effects on dopamine levels[33]. Therefore, it is possible that different drugs can either worsen or ameliorate bruxism, depending on the specific working mechanisms. Hence, different effects on bruxism can occur when analyzing the LEDD in total or for each prescription drug individually. However, it is not desirable to ignore the coherence of the subscribed drugs in this specific population. Therefore, the total LEDD score was calculated per participant.

Different studies showed different mean LEDD scores, varying from 804mg (SD± 364) to 1409mg (SD± 605)[34-37]. These differences are possibly due to geographical differences or differences in disease stage. In the present study, the mean LEDD score was 710.8 (SD±469.8). This relatively low mean score is possibly due to the low mean time since PD diagnosis in the present study: 6.7 (SD±5.9) years. This low mean LEDD score might implicate that PD symptoms and dopaminergic medication usage were not likely to cause pronounced side effects as compared to patients who have been diagnosed with PD a long time ago and/or have higher LEDD values. Besides, when chronic depression of dopamine is present, high doses are required to achieve symptom relief. These enhanced maladaptive changes could lead to levodopa-induced dyskinesia. When this

appears in the orofacial area, it can be confused with bruxism and vice versa[38]. The mix-up with orofacial levodopa-induced dyskinesia and the low LEDD scores could have led to the rejection of the hypothesis of the present study. In future studies, patients with a longer duration of PD, and thus a probably longer use of dopaminergic medication, should be included. However, such individuals are probably not capable of visiting Parkinson Cafés and/or do not use social media, and are for that reason probably not included in the present study.

Bruxism and other associated factors

Several studies have shown an association between both circadian manifestations of bruxism and TMD pain. However, also contradictory results exist[39,40]. In the present study, it was found that in this PD population, awake bruxism was significantly associated with TMD pain, while sleep bruxism only showed a trend towards an association with TMD pain. This difference can be due to the fact that in the present study, awake bruxism was reported almost 50% more often than sleep bruxism. The association between (awake) bruxism and TMD pain in this population could be explained by the fact that the load-bearing capacity (i.e., the physical capacity of individuals to endure muscle-induced load on the structures of the masticatory system) of patients with PD can be reduced, which can result in TMD pain. Besides, pain, in general, is a common non-motor symptom that is present in PD and can also be present in the orofacial area[41]. PD patients can experience different types of pain, such as musculoskeletal pain (40-75%), but also neuropathic pain. The latter can imply that pain processing in PD patients, in the peripheral or central nervous system, can be amplified[41]. However, in 6-OHDA-treated rats (i.e., rats used as PD model), bilateral mechanical hypernociception showed a reduction when undergoing dopaminergic therapy[42]. This could implicate that dopaminergic therapy could reduce nociception and therefore pain perception in patients with PD.

While bruxism during wakefulness and bruxism during sleep are commonly considered two separate entities, in the present study a co-occurrence between awake and sleep bruxism was observed. It is noteworthy that even based on the current definition of generic bruxism there is a clear distinction between awake and sleep bruxism, based on the assumption that both conditions do not share the exact same pathophysiology[4]. Nevertheless, there are, for example, psychosocial aspects related to both awake and sleep bruxism that may explain their association[43]. Therefore, the possibility of a co-existence between both circadian manifestations must be taken into account when interpreting awake and sleep bruxism in the future.

Both awake and sleep bruxism showed an association with self-reported tooth wear. The predicted prevalence of severe tooth wear according to different studies ranged between 12 and 17% in participants of 65-70 years of age[44,45]. A recently published narrative overview described that tooth wear is associated with sleep bruxism; not with awake bruxism46. This can be explained considering that during wakefulness clenching occurs more frequently than tooth grinding, which can result in less tooth wear. The difference with the general population is the higher prevalence of both sleep bruxism and awake bruxism in PD patients. Besides, there is a possibility that during wakefulness, not only clenching but also tooth grinding is present in patients with PD, due to the involuntary

movements. Furthermore, other factors that can influence the amount or severity of tooth wear[46] are also common in patients with PD (viz., polypharmacy and gastro-oesophageal reflux disease)[47,48].

Limitations of the study

This study has several limitations, due to which an association could have been missed between LEDD and bruxism. According to the international consensus, based upon self-report a definite diagnosis of bruxism cannot be established[49]. Hence, in the present study, only a diagnosis of possible bruxism could be established. Consequently, one has to be careful when interpreting the current findings. However, the advantage of self-report is evident, viz., that assessing a larger sample is feasible, as opposed to the usage of instrumental techniques that are required for establishing definite diagnoses of awake and sleep bruxism (viz., electromyography, polysomnography)4. In future studies, a multimodal assessment could improve the understanding of bruxism in this population[50]. Concerning tooth wear, the answers given by participants were subjective. Collecting objective tooth wear data in future clinical studies will improve the validity of these results. Furthermore, the questions were formulated in such manner that they lacked time sensitivy regarding complaints in the orofacial area and bruxism behaviour. Therefore, it is possible that these complaints and this behavior had already evolved before the start of the medication intake, which could have resulted in some false positive responses. To overcome these limitations, future studies should take time-sensitive aspects into account. Another limitation of the present study is the large number of missing data (42%), because reports of medication usage were frequently ambiguous or incomplete. A possible explanation is the difficulty with writing by hand and/or the amount of work participants experienced while completing the questionnaire. Therefore, the data must be interpreted with caution. Furthermore, selection bias could have been possible due to the location where this study was conducted (Parkinson Cafés and social media). The severity of the disease may therefore be lower than in the overall population of patients with Parkinson's Disease in The Netherlands. Finally, this study concerns a secondary analysis of an earlier published pilot-study[17]. In general, a disadvantage of such analysis could be that data is outdated. However, the advantages are clear, viz., cost- and time-efficiency as well as making optimal use of data that were collected from vulnerable participants which could be considered an ethical plus. Besides, this is the first study that calculated the LEDD scores and analyzed them in the association with bruxism. Nonetheless, for further research, the authors would like to suggest that the LEDD scores are calculated based on data on medication usage provided by the pharmacist or neurologist for a more reliable outcome and fewer missing values.

Conclusion

The prevalence of possible (i.e., self-reported) awake bruxism and sleep bruxism in patients with PD was high, viz., 46.0% and 24.3%, respectively. No association was found between dopaminergic medication usage and possible (i.e., self-reported) bruxism. Further, in a population with PD patients, co-occurrence of both circadian manifestations of bruxism is present. Besides, both conditions are associated with self-report of tooth wear. Finally, only possible awake bruxism was found to be associated with TMD pain; not possible sleep bruxism.

Disclosure: not applicable

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Ethical approval: the study was performed in accordance with the 1964 Helsinki Declaration. Approval was granted by the Medical Ethics Committee of the VU Medical Centre, Amsterdam, The Netherlands (file no. 2015.461; approval date November 26th, 2015).

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Tables

Table 1. An example of a medication list, aligned to 100mg of immediate-release levodopa with the use of conversion factors of different types of dopaminergic medication.

Dopaminergic medication	Total daily dose (mg)	Conversion Factor	Subtotal LEDD (mg)
Immediate release Levodopa	300	1	300
Levodopa slow release	400	0.75	300
Ropinirole	-	20	-
Pramipexole	-	100	-
Pergolide	-	100	-
Bromocriptine	-	10	-
Rotigotine	4	30	120
Amantadine	-	1	-
Apomorphine	-	10	-
Selegiline or Rasagiline	-	Total amount levodopa dosage x 0.1	-
COMT-inhibitors	800	Total amount levodopa dosage x 0.2	144 *(720x0.2)*
Total LEDD			864

Table 2. Demographic information and prevalences of the independent variables (including missings) of the included participants with PD (N=395).

			Missings (N)
Gender [N (%)]	Male	232 (58.7%)	0
	Female	163 (41.3%)	0
Age [M,SD]		67.9, SD ± 8.6	4
Time since PD diagnosis [M,SD]		6.7, SD ± 5.9	77
Dopaminergic medication dose, LEDD [M, SD]		710.8, SD±469.8	166
Sleep bruxism [N (%)]		84 (24.3%)	49
Awake bruxism [N (%)]		161 (46.0%)	45
TMD pain [N (%)]		112 (29.5%)	15
Locks [N (%)]		46 (12.3%)	21
Tooth wear [N (%)]		151 (47.6%)	78

Note |N=number of participants; M=mean; SD=standard deviation

Table 3. Single and multiple regression analysis of variables associated with possible awake bruxism in patients with PD (N=281). The associated p-value and Odds-ratio (OR) with 95%-confidence interval (CI) are presented.

Independent variable	Single regression		Multiple regression		
	P-value	Odds-ratio [95%-CI]	P-to-exit value	P-value	Odds-ratio [95%-CI]
Gender	0.422	1.19 [0.78-1.83]			
Age	P<0.001	0.94 [0.92-0.97]	0.103		
LEDD	0.736	1.00 [0.99-1.00]			
Time since PD diagnosis	0.161	0.97 [0.93-1.01]			
Sleep Bruxism	P<0.001	11.50 [6.02-21.99]		P<0.001	8.52 [3.56-20.40]
TMD pain	P<0.001	6.78 [3.97-11.58]		P<0.001	4.51 [2.31-8.79]
Locks	P<0.001	3.83 [1.91-7.71]	0.111		
Tooth wear	P<0.001	4.98 [3.03-8.17]		0.044	1.87 [1.02-3.43]

Note | R^2 = .394 (Nagelkerke), .294 (Cox&Snell). X^2 (3)=97.8, p<0.001

Table 4. Single and multiple regression analysis of variables associated with possible sleep bruxism in patients with PD (N=283). The associated p-value and Odds-ratio (OR) with 95%-confidence interval (CI) are presented.

Independent variable	Single regression		Multiple regression		
	P-value	Odds-ratio [95%-CI]	P-to-exit value	P-value	Odds-ratio [95%-CI]
Gender	0.002	2.24 [1.36-3.68]	0.124		
Age	P<0.001	0.94 [0.91-0.96]	0.394		
LEDD	0.834	1.00 [0.99-1.00]			
Time since PD diagnosis	0.551	1.01 [0.97-1.06]			
Awake bruxism	P<0.001	11.50 [6.02-21.99]		P<0.001	9.48 [4.24-21.19]
TMD pain	P<0.000	4.65 [2.74-7.88]	0.057		
Locks	P<0.001	3.81 [1.96-7.41]	0.484		
Tooth wear	P<0.001	16.64 [7.26-38.13]		P<0.001	12.49 [4.97-31.38]

Note | R^2 = .48(Nagelkerke), .32 (Cox&Snell). X^2 (2)=109.5, p<0.001

Chapter 9

Parkinson's disease, temporomandibular disorder pain and bruxism and its clinical consequences: a protocol of a single-centre observational outpatient study

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Abstract

Introduction: a recent questionnaire-based study suggested that bruxism and painful temporomandibular disorders (TMD pain) may be more prevalent in Parkinson's disease (PD) patients compared to controls. The presence of both bruxism and TMD pain may negatively influence patients' quality of life. The present study is designed to clinically and more objectively investigate the presence of bruxism and TMD pain in PD patients. The secondary aim of the study is to identify factors associated with bruxism and TMD pain in PD patients, such as disease severity and dopaminergic medication usage. Furthermore, the presence of tooth wear in PD patients will be studied as this can be a major consequence of bruxism. Finally, deviations in saliva composition that may contribute to tooth wear will be studied.

Methods and analysis: this is a single-centre observational outpatient study at the Amsterdam University Medical Centres, location VUmc. All patients with a clinical diagnosis of PD will be eligible for inclusion. Participants will fill in a set of questionnaires. Subsequently, patients will be examined clinically for, amongst others, TMD pain, presence and severity of tooth wear, and deviations in saliva composition. Sleep-time registrations will take place for 5 nights with the GrindCare® GC4 (i.e., a portable, single-channel electromyographic recorder) to assess sleep bruxism and simultaneously by the use of the BruxApp for 5 days to assess awake bruxism. We will partly use data collected during standard clinical care, to minimize patient burden.

Ethics and dissemination: the scientific and ethical aspects of this study protocol have been approved by the Medical Ethics Review Committee of the Amsterdam UMC, location VUmc; NL. 2019.143). Informed consent will be obtained from all participants. The results will be published in a peer-reviewed journal, if relevant presented at conferences, and published as part of a Ph.D. thesis.

Keywords: Parkinson's disease, epidemiology, motor neurone disease, oral medicine

Introduction

Parkinson's disease (PD) is a neurodegenerative movement disorder characterized by motor symptoms, in particular rigidity, bradykinesia, and tremor[1,2]. Patients with PD do not solely experience motor symptoms, but also non-motor symptoms like anxiety, depression, sleep problems, and cognitive dysfunction[3,4]. Besides, pain has been reported as one of the most troublesome non-motor symptoms in PD patients, early in their disesease, which could affect patients' quality of life[5,6].

Due to global ageing, the prevalence of PD is estimated to increase significantly in the near future. Ageing is associated with oral health-related issues, which may therefore occur more frequently in the near future as well[7]. Dentists regularly see patients with bruxism in the dental office, which is an oral health-related issue that is not necessarily associated with systemic diseases. Bruxism is currently defined as "a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible"[8]. It can occur during sleep, indicated as sleep bruxism, or during wakefulness, indicated as awake bruxism[8]. Not only bruxism itself, but also its possible consequences, such as mechanical tooth wear and temporomandibular disorders (TMD), have hardly been studied in patients with PD. TMD is a collective term embracing disorders of the temporomandibular joint, masticatory muscles, and adjacent anatomical structures[9]. TMD can present as painful and non-painful conditions. Patients with TMD can report, for example, orofacial pain (including headache), limitations in the movement of the mandible, and joint noises[9]. Both tooth wear and TMD may affect the oral health-related quality of life[10].

In a population with PD patients, oral health was recently studied[11]. It was shown that the oral health in PD patients is deteriorated as compared to their peers without PD. Besides, medication usage can influence salivation production, which in turn influences the oral environment[12]. Also, gastrointestinal problems are more frequently shown in patients with PD. In turn, this could influence the presence of tooth wear due to reflux[13,14].

While oral health in PD has not been studied widely[11], oral (dys-)function in PD has been studied even less, even though PD, bruxism, and TMD have been suggested to share several common characteristics (see Figure 1). Similar to PD, bruxism is considered to be regulated centrally and not peripherally[15]. In addition, in the pathophysiology of both PD and bruxism, the brain dopamine system plays an important role[16-18]. Besides, sleep disturbances[19] that are present both in PD[20] and in sleep bruxism, are associated with arousal activity[19,21]. As a result of such arousal activity, sleep bruxism may occur more frequently in people with sleep disturbances than in those without[21]. Also, in the prodromal phase of PD, a higher rhythmic masticatory muscle activity (RMMA) on polysomnography in NREM sleep has been observed, compared to controls[22]. This is a characteristic that is also seen in sleep bruxism patients[23]. Furthermore, bruxism may be considered as a risk factor for TMD, depending on the assessment methods used[24]. TMD itself shares some characteristics with PD. For example, musculoskeletal pain (of which TMD pain is a subtype) is frequently reported by patients with PD[3,25]. Finally, suggestions have been put forward that alterations in the dopaminergic system are also present in patients with pain in the orofacial region[26], although this remains to be confirmed in patients with TMD pain.

Recently, a questionnaire-based pilot study in 368 patients with PD and 340 controls suggested a higher prevalence of bruxism and TMD pain in patients with PD[27]. Also, PD patients reported a higher mean TMD-pain intensity than controls[27]. Besides, a large Taiwanese study showed a two-fold increased risk of TMD in patients with PD as compared to controls[28]. However, because of the limitations of the described studies (e.g., questionnaire-based study[27]; no international validated clinical examination used; no detailed explanation of the clinical examination given; and only newly diagnosed TMD-patients included)[28], extrapolation of these findings requires further verification through clinical and instrumental data. Hence, to overcome some of the limitations, the present protocol was designed. The planned study will acquire more objective clinical and instrumental measures for awake and sleep bruxism and TMD pain, which can give more valid information on outcomes like the presence of bruxism in this population. Also, additional factors, such as the severity of PD and cognitive function, will be included as possible predictors for bruxism and/or TMD pain in PD patients. Knowledge of the factors that can influence bruxism and/or TMD pain in patients with PD will help dentists and other oral health care providers to provide individualised care to prevent and/or alleviate symptoms of bruxism and/or TMD pain and their consequences in this vulnerable group of patients.

Based on the above-summarized evidence, the primary aim of this study is to investigate the presence of bruxism and TMD pain in PD patients, through objective clinical and instrumental measurements. Based on our pilot-study outcomes[27], we hypothesise that the prevalence of bruxism and TMD pain in the current population will be higher than in their peers without PD, as described in the literature[29,30].

In addition, the secondary aims and their corresponding hypotheses are the following:

1. To identify which factors are associated with bruxism and TMD pain in PD patients. We hypothesise that factors like medication usage[16], disease severity[15,17], psychosocial factors[31-33], and lifestyle factors[31,32,34] are influencing the studied associations.
2. To investigate whether the salivary flow, the pH, and the buffer capacity of saliva in patients with PD are related to the severity of tooth wear. Our hypothesis is that in patients with PD, the saliva composition and salivary flow deviate from normal standards and that this is associated with the severity of tooth wear[14].
3. To investigate with Dopamine Transporter Single Photon Emission Computed Tomography (DAT-SPECT) whether there is a relationship between the degree of presynaptic dopaminergic loss and the presence of bruxism in these patients. The hypothesis is that there is a difference in striatal dopaminergic deficit between PD patients with and without bruxism, in which patients without bruxism show a smaller deficit.

Methods and analysis

The design of this study is a single-centre observational outpatient study that will take place at the Department of Neurology of the Amsterdam University Medical Centres (Amsterdam UMC), location VUmc. The data collection will take place for two years. Due to the COVID-19 pandemic, the start date is delayed. However, the estimated start and end dates will be January 2023 and January 2025, respectively.

Participants and eligibility

Patients already clinically diagnosed with PD or planned for an intake appointment with presumable PD at the outpatient clinic for movement disorders of the VUmc, will be eligible to participate in the study. Yearly, about 100-120 new consultations for PD are seen in the outpatient clinic. In addition, patients already receiving treatment at the VUmc are eligible for participation as well. The inclusion and exclusion criteria are listed in Table 1.

Study procedure

In Figure 2, the study procedure is visualized. If patients agree to participate in the study, they will be asked to sign an informed consent. This study will be performed in parallel to the routine clinical care (see Table 2) at the Amsterdam UMC, location VUmc. When questionnaires/screenings were filled in ³ 1 year ago, participants will be asked to repeat this. Specifically, for this study, additional information will be obtained in the form of a set of questionnaires that participants can fill in at home and of a clinical examination at the hospital (see Table 3). The neurologist will determine whether additional brain imaging (viz., MRI or DAT-SPECT) is necessary, mainly in cases of clinical doubt. The estimated percentage of additional brain imaging in newly referred patients is 40%.

Main study parameters

The main study parameters or endpoints are "presence of bruxism (sleep and/or awake)" as well as "diagnosis of TMD pain". For the assessment of sleep bruxism, patients will be asked to sleep 5 complete registration nights with a portable, single-channel electromyographic recorder, viz., the GrindCare® GC4 (Sunstar Suisse SA, Etoy, Switzerland)[58,59]. For the assessment of awake bruxism, patients will use, for 5 complete registration days, the BruxApp[57,60], which is a mobile application for the recording of bruxism activity based on ecological momentary assessment[8]. According to international consensus, a classification of the probability that bruxism is present can be made as follows: possible, probable, and definite bruxism presence[61]. In this research, all probabilities of bruxism presence can be determined, however, the highest probability will be used (viz., both probable and definite). When patients cannot use the GrindCare® GC4 and/or BruxApp, and more certainty towards a definite presence is thus impossible, probable bruxism presence will be determined with the use of data from the clinical examination, based on the presence of positive symptoms of bruxism (viz., clenching marks in the soft tissues of the cheek, tongue, or lip, mechanical tooth wear (attrition), and/or hypertrophy of the masseter muscle)[61]. Differences in PD symptoms between those who can, and those who cannot complete the instrumental assessments will be tested as to gain insight into the external validity or generalizability of the conclusions involving bruxism modeling.

The TMD-pain diagnosis will be established according to the Diagnostic Criteria for TMD (DC/TMD)[50], with the use of standardized questionnaires and clinical examination procedures. Based on the collected data, the following diagnoses can be set: myalgia (local myalgia, myofascial pain, myofascial pain with referral), arthralgia, headache attributed to TMD, and non-painful joint disorders (disc displacement with reduction, disc displacement with reduction with intermitted locking, disc displacement without reduction with limited mouth opening, disc displacement without reduction without limited mouth opening, degenerative joint disease, subluxation). The main focus of this research protocol will be the TMD-pain diagnosis, for the establishment of which the diagnostic flow chart of the DC/TMD will be used[50].

Dentists making clinical assessments for bruxism or TMDs will blinded to the results of the instrumental assessments (i.e., GrindCare® GC4 and BruxApp for sleep bruxism and awake bruxism, respectively).

Secondary study parameters

To identify which factors are associated with bruxism and TMD pain in PD patients, several variables will be evaluated (see Tables 2 and 3), using different clinical/instrumental measures (see appendix 1-3). Most of these variables have already been reported as possible risk factors for bruxism[32] and/or TMD[62] in the general population[31-33]. However, the variables dopaminergic medication usage and disease stage/severity of PD have not been studied yet in the association with bruxism or TMD pain in PD patients. Finally, if DAT-SPECT imaging is available, we will compare the measured presynaptic striatal dopaminergic deficit between participants with and without bruxism[46].

Sample size

According the pilot study, the prevalence of awake bruxism, sleep bruxism, and TMD pain in patients with PD is 46%, 24%, and 29.5%, respectively[23]. Taking the cautious approach, we calculated the sample size for awake bruxism, sleep bruxism, and TMD pain and chose the largest sample size. Aiming for a precision of 5% with a level of confidence of 95%, 246 participants are needed[63]. See appendix 2 for the sample size calculation. Furthermore, the approach to calculate the sample size for the most important secondary aim (viz., to identify which factors are associated with bruxism and TMD pain in PD patients) is also shown in appendix 2. The numbers are obtained when reaching the sample size for the primary aim.

Statistical approach

With the use of descriptive tests, demographic data will be summarised. In Figure 3, it is shown how the dataset is analysed to give an answer on which factor is associated with the presence/absence of probable bruxism/TMD pain or with the frequency (i.e., the number of bruxism events per hour) of definite bruxism. The forward selection procedure will be used for the (strongest) independent variables (see Table 4) until all variables in this regression model show a P-value <0.05 (See Step 2, Figure 3). Finally, to analyse if there is an association between tooth wear and composition of saliva, Spearman's correlation coefficient will be used. For the DAT-SPECT, a semi-quantitative analysis will

be used. Ratios for specific versus non-specific binding will be calculated for the regions of interest (viz., left and right putamen and caudate nucleus, using the occipital cortex as a reference area) and analysed using the independent sample t-test[46,47].

Patient and public involvement

Neither patients nor the community were involved in the design of this study. However, feedback from participants of the earlier pilot study[23] was used to design this study. Patients with PD will be involved in the performance of the study. The burden for the participants will be kept as minimal as possible. On request, the outcomes of this study will be disseminated to the participants.

Discussion

The primary aim of this study is to objectively measure the presence of bruxism and TMD pain in a population of patients with Parkinson's Disease (PD). Furthermore, the three secondary aims are described as follows: (i) to identify which factors are associated with bruxism and TMD pain in PD patients, (ii) to investigate whether the salivary flow, the pH, and the buffer capacity of saliva in patients with PD are related to the severity of tooth wear, and finally (iii) to investigate with DAT-SPECT whether there is a relationship between the degree of presynaptic dopaminergic loss and the presence of bruxism in these patients.

To the best of our knowledge, this is the first study that attempts to objectively measure the presence of awake bruxism, sleep bruxism, and TMD pain in a population of patients with PD. Previous studies investigated the prevalence of awake bruxism in this population, however only few participants were included or only questionnaires were used[23,64]. When quantifying bruxism with continuous data, recent insights showed a better quality of a definite bruxism diagnosis[61]. Nevertheless, we used a dichotomous outcome in this protocol study to answer our first aim, i.e., to investigate the presence of bruxism. Besides, we also included self-report and clinical data, which do not yield continuous outcomes. Despite this, in the present study, the use of the GrindCare® GC4 and the BruxApp can give more certainty towards a definite establishment of sleep and awake bruxism, respectively[61]. This enables the analysis of continuous outcomes, which has been suggested by several authors[65,66]. However, as mentioned earlier, not every participant will be able to use the GrindCare® GC4 and/or the Bruxapp. Therefore, this protocol is designed to include all probability levels for the assessment of bruxism, which contributes to the feasibility of this protocol[61] Importantly, participants able to complete all assessments may differ from those who cannot complete instrumental assessments due to differences in severity of their PD symptoms. Fine motor problems which occur in PD create barriers for electrode placement and cell phone use as required for instrumental assessments of sleep and awake bruxism. Therefore, we will test for PD symptom differences between subgroups defined by comparing participants completing or not completing instrumental assessments. If differences are found, this will indicate limitations to the external validity or generalizability of conclusions involving bruxism modeling.

In addition, the clinical examination according to the DC/TMD[50] enables setting a valid TMD-pain diagnosis, making a distinction between several TMD complaints, and comparing the outcomes with other (inter-) national research. An important aspect of a TMD-pain diagnosis according to the DC/TMD is that it considers the aspect of "familiar pain" as part of the diagnostic algorithm. As such, PD-related pain characteristics like pain exacerbation due to "wearing off" of dopaminergic medication and lower pain thresholds in individuals living with PD as compared to similar individuals without PD[67], will be taken into account.

Because PD patients are vulnerable and burdened with frequent visits to multiple caregivers (e.g., their neurologist, physiotherapist, and speech therapist), it is important to burden the participants as minimally as possible. Therefore, during the process of designing this study and collecting the data, a multidisciplinary approach was established between neurologists and dentists to enable an as efficient as possible usage of the patient's time and energy.

The targeted number of inclusions will be a challenge. However, the calculated sample size is an estimation, because no clinical prevalences are known as yet. Like in otherwise healthy individuals, clenching and grinding are not always recognized by the patients themselves[68,69], thus the prevalence of sleep bruxism in the pilot study could have been underestimated. This means that the calculated sample size in this study might be higher than eventually required. Therefore, an interim analysis will be performed after 130 included participants or 6 months.

This study has no longitudinal character and therefore, no causal relations can be observed between the (in-) dependent variables. Also, polysomnography is the golden standard to detect sleep bruxism while in the present study, a portable electromyographic recorder will be used[61]. However, since this device will be used for several nights in a row, the fluctuating character of sleep bruxism can be taken into account and is therefore considered a good proxy for definite sleep bruxism[59]. It should be noted, however, that the portable recorder will fail to enable a distinction between jaw-muscle activities related to sleep bruxism and those related to other orofacial movement disorders like oral dyskinesia and oro-mandibular dystonia[70]. This is an important issue, because such movement disorders can be present in patients with PD related to their medication usage. In fact, in their updated international consensus paper on bruxism, Lobbezoo et al. (2018) added the phrase that bruxism is a masticatory muscle activity in "otherwise healthy individuals"[61]. People living with PD are certainly not "otherwise healthy". In the later stages of levodopa-treated PD, dyskinesias, including oral dyskinesias, commonly occur[70]. Hence, the question could be raised if the masticatory muscle activity observed in people with PD is "bruxism" at all. This calls for caution in the interpretation of the bruxism-related findings of this study. Fortunately, in the questionnaire and clinical examination of the MDS-UPDRS[39] (Table 2), the presence of oral dyskinesia and oro-mandibular dystonia is included. Hence, it is possible to correct for their presence in the data analysis.

This study does not include a control group. This limits the interpretation of whether the prevalence of bruxism or TMDs is low or high in people with PD, which will only be possible by comparing the

findings with prevalences as reported in the literature. In addition, since tooth wear in older people reflects a lifetime of factors, it will be also difficult to interpret the tooth wear findings in people with PD without having the possibility for a direct comparison with similar individuals without PD. Also in this case, comparisons should be sought with literature data. These issues should be considered limitations of this study.

In conclusion, this study will give more detailed information about the presence of bruxism and TMD pain in patients with PD, as well as about possible associated factors like medication usage and severity of the disease. Finally, more clinically relevant information will become available for dentists and other oral health care professionals about the amount of tooth wear and the composition of saliva in patients with PD.

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Data availability: Due to the sensitive nature of personal information, all data will be blinded and stored in secure environments. Only the executive researcher and the head of the department can reach the unblinded informed consents and the key for unblinding. These are stored separately. Digital data will be stored pseudonymized in a secure database using Castor EDC (CDISC, Amsterdam, Netherlands). Detailed methods for data management and storage can be obtained by contacting the corresponding author.

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Ethical approval: The scientific and ethical aspects of this study protocol have been approved by the Medical Ethics Review Committee of the Amsterdam UMC, location VUmc; NL. 2019.143). Informed consent will be obtained from all participants. The results will be published in a peer-reviewed journal, if relevant presented at conferences, and published as part of a Ph.D. thesis.

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Figures and tables

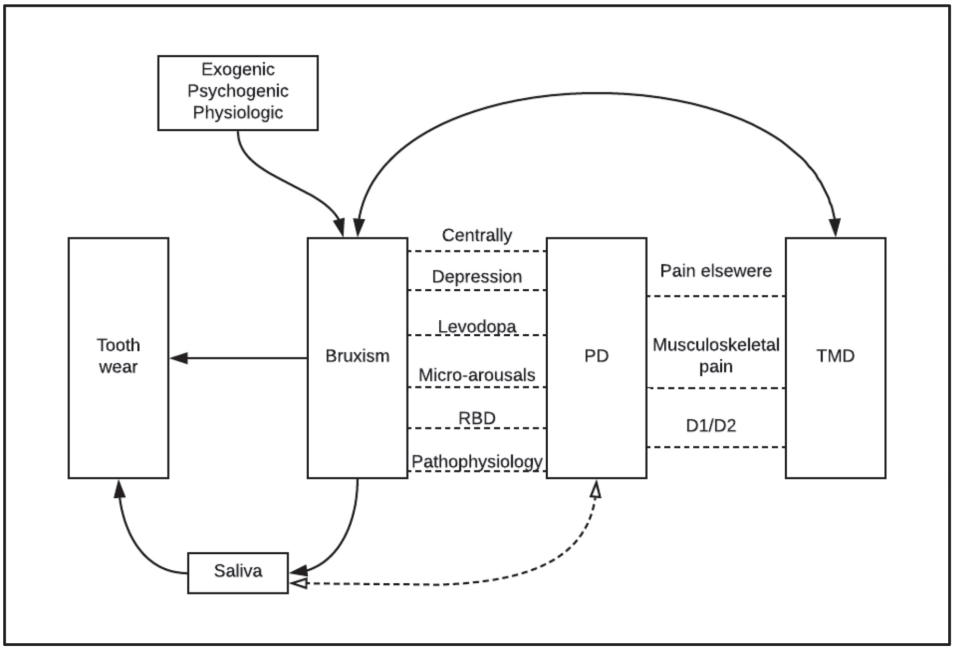

Figure 1. Visualization of the possible interactions between the different research variables. *Parkinson's Disease (PD) is associated with bruxism through different variables: the dopaminergic system (pathophysiology) plays a role in bothPD and bruxism; the prodromal phase of PD (RBD) shows the same characteristics during sleep as does bruxism; sleep disturbances lead to micro-arousals that can lead to bruxism; dopaminergic medication (levodopa) can influence bruxism; depression is one of the risk factors for bruxism and is more prevalent in patients with PD; and finally, both PD and bruxism are regulated centrally and not peripherally. PD is also associated with TMD: PD patients experience pain in the entire body (i.e., widespread pain), which is a risk factor for TMD pain; also, musculoskeletal pain (as in TMD pain) is frequently present; and finally, alterations in the striatal dopaminergic system (D1/D2 ratio) could play a role in TMD pain. Bruxism itself is a risk factor for TMD pain and vice versa. Besides, tooth wear can be a consequence of bruxism. When bruxism occurs, saliva can be increased, which can be a protective factor for tooth wear. Also, saliva can be changed due to PD medication. Finally, several exogenic, psychogenic, and physiologic factors can be a risk for bruxism.*

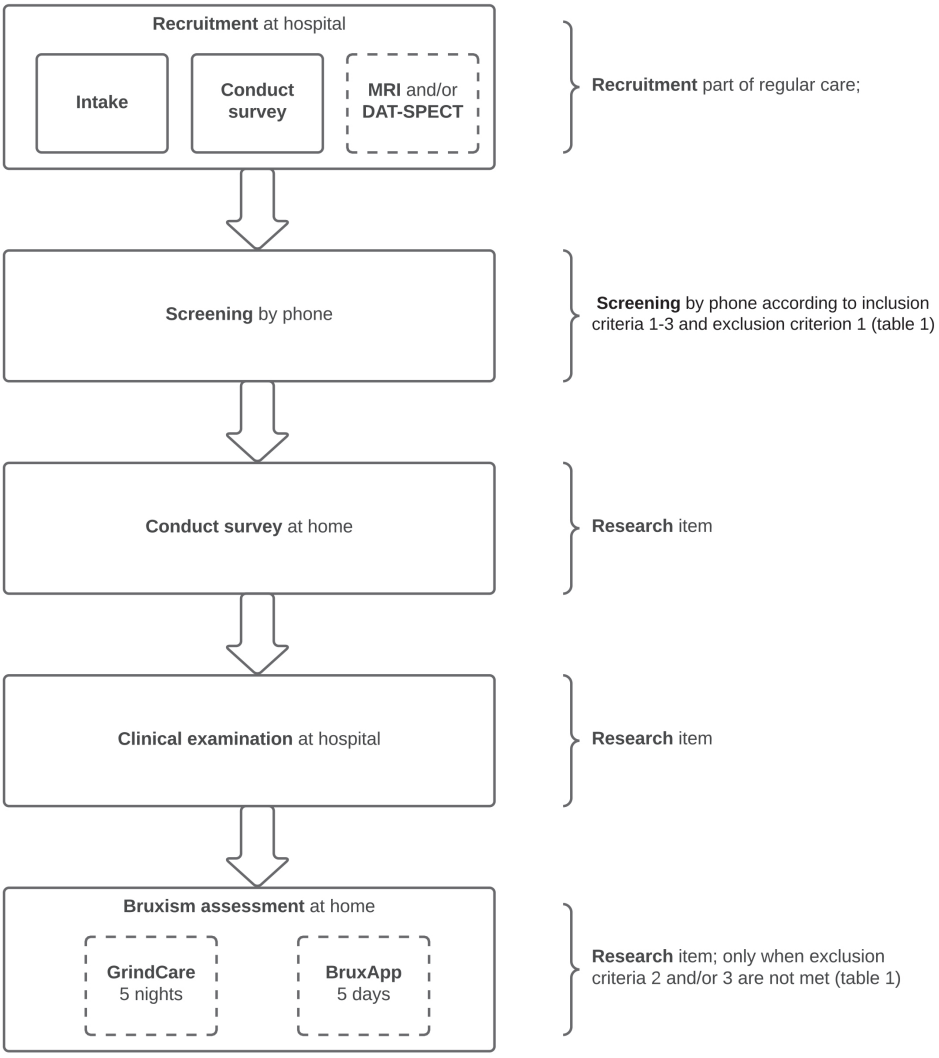

Figure 2. Flowchart of the study in which a distinction was made between the attendance of participants at the hospital and the study components at the participant's home. The intake and first survey is part of the regular care at the hospital, and only followed by an additional MRI and/or DAT-SPECT scan when indicated (dashed line). When patients are eligible and consent to participate (screening by phone), the additional data are collected after the intake. First, a questionnaire is filled in by the participants. After that, the participant is invited for the clinical examination. When questionnaires/screenings that are part of the regular care were filled in ≥ 1 year ago, participants will be asked to repeat this procedure simultaneously with the additional questionnaire and/or clinical examination. Finally, participants will sleep for 5 complete registration nights with the GrindCare for the assessment of sleep bruxism (when exclusion criterion 2 was not met) and use the BruxApp for 5 complete registration days for the assessment of awake bruxism (when exclusion criterion 3 was not met).

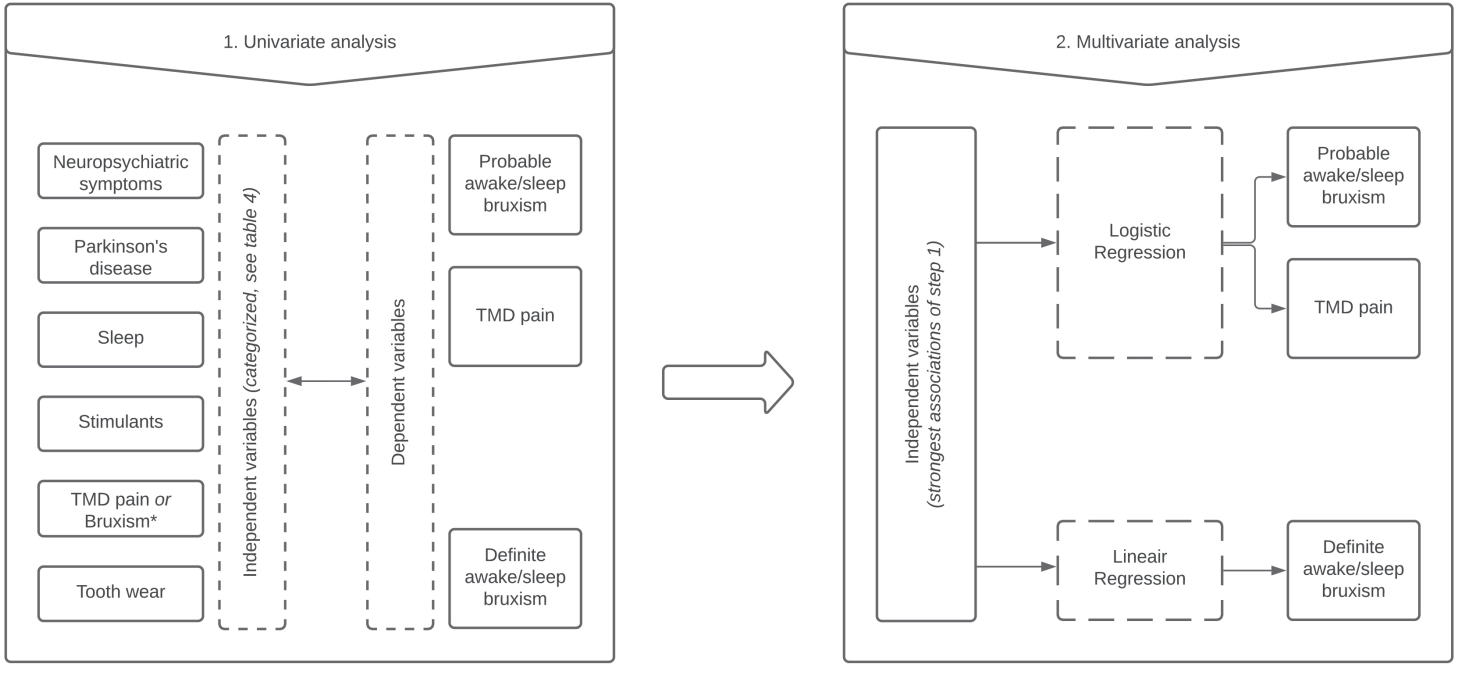

Figure 3. Flowchart of the data-analysis related to the first secondary aim: "to investigate which factors are influencing the presence of probable awake/sleep bruxism, TMD pain and the frequency of definite awake/sleep bruxism". All variables will be tested individually to see whether an association with the dependent variable (awake and sleep bruxism and TMD pain) exists, and to see how strong this association is (step 1). This dataset will be analysed for both probable bruxism and TMD pain with the use of logistic regression analyses. For definite bruxism, a linear regression analysis will be used (step 2). The forward selection procedure will be used for the (strongest) independent variables until all variables in this regression model show a P-value <0.05 (step 2). In both step 1 and step 2, a distinction will be made between sleep and awake bruxism.

Table 1. Inclusion and Exclusion criteria. When patients have a pacemaker, they cannot use the GrindCare® GC4 (i.e., a portable, single-channel electromyographic recorder to detect sleep bruxism) and will be excluded from that specific part of the study. When patients do not have a smartphone, participants cannot use the BruxApp (i.e., an application on a smartphone to assess awake bruxism) and will be excluded from that specific part of the study.

Inclusion criteria	Exclusion criteria
1. ≥18 years of age	**1.** atypical parkinsonian syndromes
2. ≥ 21 on the Montreal Cognitive Assessment (MoCA)[35]	**2**. for using the GrindCare: pacemaker
3. fulfil clinical diagnostic criteria for PD[36]	**3.** for using the BruxApp: no smartphone
	4. for the DAT-SPECT: no deep brain stimulation implant present

Table 2. Questionnaires and clinical data collected as part of the regular care at the hospital, which is used in this observational study. See Appendix 1 for a description per questionnaire/instrument.

Variables standard care hospital
1. Cognitive function (Montreal Cognitive Assessment, MoCA)[35];(Parkinson's Disease Cognitive Functional Rating Scale, PD-CFRS)[37]
2. Disease stage (Hoehn & Yahr)[38]; Disease severity (Unified Parkinson's Disease Rating Scale – III, UPDRS-III)[39]
3. Dopaminergic medication (Levodopa equivalent daily dose, LEDD)[40]
4. Neuropsychiatric symptoms: Depression (Beck Depression Inventory-ii, BDI-ii)[41]; Apathy (Apathy evaluation scale, AES)[42]; Anxiety (Parkinson Anxiety Scale, PAS)[43]; Psychotic (Parkinson's Disease-adapted scale for assessment of positive symptoms, SAPS-PD)[44]; Impulse control (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, QUIP-RS)[45]
5. Presynaptic dopaminergic loss, when applicable (brain imaging) (Dopamine Transporter Single Photon Emmission Computed Tomography, DAT-SPECT)[46,47]
6. Quality of sleep (Scales for Outcomes PD Sleep, SCOPA-SLEEP)[48]
7. Stimulants usage: Alcohol (per unit, daily), Drugs (per unit, daily), Smoking (per unit, daily)

Table 3. Additional research components, i.e., performed in addition to the regular appointments at the hospital. See Appendix 1 for a description per questionnaire/instrument.

Additional research components	
Questionnaires	1. Reflux (GerdQ-NL)[49]
	2. TMD pain (according to the Diagnostic Criteria for TMD, DC/TMD)[50] and intensity (graded chronic pain scale, GCPS)[51]
	3. Tooth wear
	4. Sleep (Obstructive Sleep Apnea, STOP-Bang NL)[52]
Clinical examination	1. Intra-oral examination (positive symptoms of bruxism (viz., clenching marks in the soft tissues of the cheek, tongue or lip, mechanical tooth wear, hypertrophy of the masseter muscle))[50]
	2. Quantitative tooth wear screening (part of the Tooth Wear Evaluation System, TWES)[53]
	3. A brief screening of the dental prosthesis (when applicable)
	4. Dry mouth screening (Clinical Oral Dryness Score, CODS)[54]
	5. Jaw-mobility examination (DC/TMD)[50]
	6. Joint noises examination (DC/TMD)[50]
	7. Palpation of masticatory muscles and temporomandibular joints (DC/TMD)[50]
	8. Dynamic/static tests [55]
	9. Bruxoprovocationtest [55]
	10. Saliva test (Saliva-Check Buffer®)[56]
Registration	1. BruxApp [57]
	2. GrindCare® GC4[58,59]

Table 4. The independent variables (categorized) that will be investigated for one of the secondary aims: which factors are associated with the presence of bruxism and TMD pain in patients with Parkinson's Disease?

Independent variables (categorized)
1. Bruxism (*when analysing which factors are associated with the presence of TMD pain in patients with PD)*
2. Neuropsychiatric symptoms (depression, anxiety, apathy, psychosis, impulse disorders)
3. Parkinson's Disease (disease stage, disease severity, medication usage, cognitive function)
4. Sleep (quality of sleep, obstructive sleep apnea)
5. Stimulants usage (alcohol, smoking, drugs)
6. TMD pain (*when analysing which factors are associated with the presence of bruxism in patients with PD)*
7. Tooth Wear related (reflux, saliva, dry mouth)

Appendix

Appendix 1| Secondary study parameters

All secondary study parameters are listed below, along with a description of the questionnaires/ instruments that will be used for their assessment.

General disease information:

- *Disease severity:* see motor symptoms.
- *Disease stage:* will be established with the Hoehn & Yahr scale. This is a 0 to 5 scale: "asymptomatic (score 0)", "only unilateral involvement (score 1)", "bilateral involvement without impairment of balance (score 2)", "light to mild bilateral involvement, some postural instability and physically independent (score 3)", "severe disability, still able to walk independent (score 4)", and "wheelchair or bed bounded without help (score 5)", in which a higher number means a more developed disease stage[1].
- *Levodopa equivalent daily dosage (LEDD):* this is, according to Tomlinson, a "summation of each individual antiparkinsonian drug aligned to 100mg immediate release L-dopa, by means of individual conversion factors"[2,3].
- *Presynaptic dopaminergic loss:* will be analysed by means of DAT-SPECT, when applicable.

Motor symptoms:

- *Motor symptoms*: will be analysed with the Movement Disorder Society Unified Parkinson Disease Rating Scale III (MDS-UPDRS III)[4]. This involves an examination of motor function, performed by an examiner (e.g., neurologist, trained nurse, or trained research assistant). The patient has to complete 18 motoric tasks. Subsequently, the examiner scores the tasks from 0 till 4: "normal (score 0)", "slight (score 1)", "mild (score 2)", "moderate (score 3)", and "severe (score 4)" motor problems for that specific part. Finally, a summation of each individual task is established, after that a classification can be made: "mild (score ≤ 32)", "moderate (score 33-58)", and "severe (score ≥ 59)" motor problems[5].

Non-motor symptoms:

- *Anxiety:* will be registered through the Parkinson Anxiety Scale (PAS)[6]. The PAS consists of 3 questionnaires (persistent anxiety, episodic anxiety, and avoidance behavior), with in total 12 questions. There are 5 response options, scored as 0 till 4: "never (score 0)", "occasionally (score 1)", "sometimes (score 2)", "frequently (score 3)", and "always (score 4)". Afterwards, 4 groups can be made: "generalized anxiety disorder (score ≥ 11 on that subscale)", "episodic anxiety (score ≥ 6 on that subscale)", "avoidance behavior (score ≥ 5 on that subscale)", and "any anxiety disorder score (score ≥ 14)".
- *Apathy:* will be measured by means of the apathy evaluation scale (AES)[7]. This scale has 14 statements, with 4 response options: "not at all (score 0)", "slightly (score 1)", "somewhat (score 2)", and "a lot (score 3)". A total sum score of 42 can be reached. When a higher score is reached, apathy plays a bigger role. The cut off point for "high apathy score" is 14 points.

- *Cognitive function:* will be analysed by means of the Montreal Cognitive Assessment (MoCA)[8,9] and the Parkinson's Disease Cognitive Functional Rating Scale**, (**PD-CFRS)[10,11]. The MoCA is a screening instrument for cognitive dysfunctions on different aspects, such as memory or language, which exist of 11 items in 8 different domains. The examiner (e.g., neurologist, trained nurse, or trained research assistant). scores each item individually. A sum score of 30 can be reached, wherein a score of 26 or above represents a normal cognitive function and a score above 21 represents a mild cognitive impairment. The PD-CFRS exists of 12 questions with four response options, scored as follows: "No (score 0)", "Sometimes (score 1)", "A lot (score 2)" and "not applicable". All questions answered with "not applicable" will be scored with the mean of all the other questions. A total score of 0-24 can be reached, a higher score means more cognitive problems. The total score will be used.
- *Depression:* will be registered through the Beck Depression Inventory (BDI-II)[12,13,14]. The BDI-II exists of 21 questions with four response options, scored as 0 till 4 (for example: "I do not feel sad", "I feel sad much of the time", "I am sad the whole time", and "I am sad or so unhappy that I can't stand it"). A maximum of 63 points can be assembled. Afterwards, 4 groups can be made: "none or minimal (score 0-13)", "light (score 14-19)", "moderate (score 20-28)", and "severe (score 29-63)" depressive symptoms.
- *Impulsive-compulsive behavior:* will be analysed by means of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS)[15]. This questionnaire has 7 subscales and in total 28 questions, with 5 response options scored 0 till 4: "never (score 0)", "occasionally (score 1)", "sometimes (score 2)", "frequently (score 3)", and "a lot (score 3)". For a combined impulse control disorder, 4 subscales are combined. A total sum score of 64 can be reached, a higher score indicating more impulsive-compulsive behavior. When 10 points or above are registered, an impulse control disorder is present.
- *Psychosis*: will be measured by means of Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD)[16]. This 9-item observer-rated scale is scored from 0 till 5: "none (score 0)", "possible (score 1)", "mild (score 2)", "mediocre (score 3)", "explicit (score 4)", and "severe (score 5)", including a part about hallucinations and a part about disillusions. A higher sum score means a probable presence of psychosis. The total score will be used.
- *Quality of sleep:* is analysed by means of two types of questionnaires that are used in this study to assess this construct. The STOP-BANG-NL[17] questionnaire that screens for the risk for moderate to severe obstructive sleep apnea (OSA), and the Scales for Outcomes PD Sleep (SCOPA-sleep)[18] that screens for quality of sleep during the night and sleepiness during the day. The STOP-BANG-NL consists of 8 questions, with 2 response options: yes (score 1) and no (score 0). The total score ranges from 0-8, a classification can be made: "low risk for OSA (score < 3)", "intermediate risk (score 3-4)" and "severe risk for OSA (≥5)"[17]. The SCOPA-Sleep questionnaire consists of 6 questions about daytime sleepiness, with 4 response options scored from 0 till 3: "never (score 0)", "sometimes (score 1)", "frequently (score 2)", and "a lot (score 3)", and 5 questions about night time sleep, with 4 response options scored from 0 till 3: "not at all (score 0)", "somewhat (score 1)", "quite (score 2)", and "a lot (score 3)"). A higher score means more daytime sleepiness and/or more nighttime sleep problems.

Oral health and dysfunction:

- *Reflux*: will be analysed with the Gastroesophageal Reflux Disease Questionnaire (GERD-Q NL)[19]. This is a self-administered questionnaire with 4 graded Likert scales scored from 0-3 for predictors of GERD, and 2 reverse Likert scales scored from 3-0 for negative predictors of GERD. The response options are as follows: "0 days (score 0 or 3)", "1 day (score 1 or 2)", "2-3 days (score 2 or 1)", and "4-7 days (score 3 or 0)" dependent on a (reverse) likert scale. When a score of ≥ 8 is reached, there is a suspicion for GERD.
- *Saliva:* based on the Saliva Check Buffer© (GC EUROPE N.V), the quantity and quality (pH and buffer capacity) of saliva will be screened[20]. The buffer capacity stands for the capability of saliva to neutralize the environment of the mouth. Both saliva in rest and saliva that is stimulated during chewing will be investigated. An overview of the normal values is given in appendix 3. Additionally, in the clinical examination, a dry mouth screening by means of the Clinical Oral Dryness Score (CODS) will be performed, which includes a 10-item observer-rated dichotomous outcome questionnaire: "present (score 1)" and "absent (score 0)". When a summation is performed, the following cut-off points are applicable: "mild dryness (score 0-3)", "moderate dryness (score 4-6)", and "severe dryness (score >6)".
- *TMD-pain intensity:* will be analysed with the use of the Graded Chronic Pain Scale (GCPS)[21]. This is a 7-item questionnaire. Six items have an ordinal scale from 0 till 10, in which 0 stands for "no pain" and 10 for "the worst pain ever". Additionally, the amount of days that where disabling because of the pain in the last 30 days are noted. When scoring, 5 classifications can be made: "no pain (grade 0)", "low disability, low intensity (grade 1)", "low disability, high intensity (grade 2)", "high disability, moderately limiting (grade 3)", and "high disability-severely limiting (grade 4)".
- *Tooth Wear:* will be analysed with the screening module of the Tooth Wear Screening Index (TWES)[22] that quantifies the amount of tooth wear in 6 sextants of the mouth (right side, front, and left side of the upper jaw and the lower jaw) from 0 till 4: "no wear (score 0)", "visible wear within the enamel (score 1)", "visible wear with dentin exposure and loss of clinical crown height of ≤1/3 (score 2)", "loss of crown height >1/3 but <2/3 (score 3)" and "loss of crown height ≥2/3 (score 4)"[23]. Additionally, the palatal side of the upper front is also graded from 0 till 2: "no tooth wear (score 0)", "tooth wear confined to the enamel (score 1)", and "tooth wear with dentin exposure (score 2)". All numbers are scored per tooth and are not summed. The highest number will be used for analysis.

Miscellaneous:

- *Lifestyle factors (smoking, alcohol, drugs):* will be gathered by means of self-report in the standard-care questionnaire of the VUmc. Use of alcohol is noted as units per week. In case of smoking and use of drugs will be both quantified as a nominal variable (participants do (not) smoke and/or use drugs).
- *Quality of life:* will be analysed with the Parkinson's Disease Questionnaire – 8 (PDQ-8)[24], by means of 8 questions about quality of life regarding PD. Participants can answer at an ordinal 5-item scale, with scores from 0 till 4: "Never (score 0)", "Occasionally (score 1)", "Sometimes

(score 2)", "Often (score 3)", and "Always (score 4)". A score from 0 till 32 can be reached. When a higher score is applicable, poor health-related quality of life is present. The total score will be used.

- *Somatic symptoms*: will be analysed with the Patient Health Questionnaire – 15 (PHQ15)[25]. Severity of somatization is evaluated by means of 13 questions about somatic symptoms divided in 3 subscales, with scores 0 till 2: "not at all (score 0)", "bothered a little (score 1)", and "bothered a lot (score 2)". Additionally, two questions about sleep and tiredness are present, which are also divided in 3 subscales with scores 0 till 2: "not at all (score 0)", "several days (score 1)", and "more than half of the days/nearly every day (score 2)". Scores of 0, 5, and 15 are the cut-off points for "low", "median", and "high somatic symptom severity", respectively.

Appendix 2| Sample size calculation

The following formula was used for the sample size calculation:
$n = (Z^2P(1-P))/d^2$
Z = Z statistic for a level of confidence
P = expected prevalence or proportion (in proportion of one)
d = precision
For the level of confidence of 95%, Z value is 1.96.
With an assumed prevalence of 46% (WB according pilot study), P is 0.46
With a precision of +/-5 percentage points (0.05), *d* should be set at 0.05.

The numbers for the secondary aims are obtained when reaching the sample size for the primary aim. The approach for the sample size calculation of the secondary aims are as follows:
Since no clinical data of the variables that will be studied are available yet in a population with PD, an effect size is not known for our outcome measures. Nevertheless, in a recent questionnaire-based study, an association between PD on the one hand and bruxism and TMD pain on the other was reported[26]. The prevalence found for these outcome measures where 46.0%, 24.3%, and 29.5% for awake bruxism, sleep bruxism, and TMD pain, respectively. In the current study, a total of 6 independent categorized variables (see Table 4) will be analysed to determine if they are associated with the presence of probable and definite bruxism and/or TMD pain in patients with PD, by means of logistic and linear regression analyses (see statistical approach). We assume that only four predictors will be eligible for multivariate analysis, because (i) only predictors with the strongest associations are included, and (ii) predictors will drop out due to their probable association with each other. The literature about numbers of observations in participants per variable (events) in a logistic regression analysis indicated that for each predictor in a regression analysis, data from 10-20 events is needed[27]. Consequently, 15 events are chosen and thus (4x15=) 60 events are needed. Based on the prevalence of the recent questionnaire-based pilot study[26], a minimum of 130 participants (60 events/0.46 (= prevalence of awake bruxism)) and a maximum of 246 participants (60 events/0.243 (=prevalence of sleep bruxism)) are needed[26]. For the linear regression, this estimate of the sample size is sufficient to detect medium and large effect sizes[28]. Because this is a wide range, an interim analysis will be done after the inclusion of at least 130 participants or a maximum of 6 months.

Appendix 3|Cut off points for Saliva Check Buffer (GC EUROPE N.V), to determine whether the quantity and composition of saliva deviate from normal values.

Saliva type	Volume (ml)	interpretation	pH	interpretation	Buffercapacity	Interpretation
During rest	1. >0.50 2. 0.50-0.25 3. 0.24-0.10 4. <0.10	1. Hypersalivation 2. Normal 3. Risk 4. Pathologic	1. >7.5 2. 7.5-6.8 3. 6.7-6.5 4. <6.5	1. Abnormal 2. Normal 3. Risk 4. Pathologic	1 10-12 2. 6-9 3. 0.5	1. Normal/high 2. Low 3. Very low
During chewing	1. >2.00 2. 2.00-0.75 3. 0.74-0.50 4. <0.50	1. Hypersalivation 2. Normal 3. Risk 4. Pathologic	1. >8.0 2. 8.0-7.0 3. 6.9-6.5 4. <6.5	1. Abnormal 2. Normal 3. Risk 4. Pathologic	1. 10-12 2. 6-9 3. 0-5	1. Normal/high 2. Low 3. Very low

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Chapter 10

Discussion

Discussion

Although "trembling" thoughts remain, the studies described in this PhD thesis have deepened our insight into the oral health, in its broadest sense, of Parkinson's disease (PD) patients. The general aim of this thesis was to further our knowledge on the umbrella term "oral health", including oral hygiene, oral health and diseases (e.g., gingivitis, periodontitis, tooth decay, and tooth loss), and orofacial pain and dysfunction (e.g., TMD pain, limited jaw movements, and bruxism) in patients with PD. In summary, compared to healthy controls, oral health is worse in PD patients (chapter 2), and they experience more orofacial pain and dysfunction (chapters 6, 7, and 8). In addition, less salivary flow and subjective complaints of a dry mouth and/or drooling are more prevalent in PD patients than in healthy controls (chapter 3). Most likely as a consequence of this, PD patients report a worse oral health-related quality of life (OHRQoL) than healthy controls (chapter 4). Lastly, dental practitioners experience that the oral health care system is currently not adequately equipped for the treatment of PD patients. They reported opportunities for improvement in the areas of treatment, organisation, research, and education (chapter 5). In this general discussion, we first briefly reflect on our studies' confirmatory and novel findings, organised per main topic (viz., oral health and diseases, and orofacial pain and dysfunction). Thereafter, we give an overview of the remaining knowledge gaps and newly raised questions after writing this thesis. We conclude the chapter with a discussion of the implications of the findings presented in this thesis for clinical practice, future research, and education.

Oral health and diseases: confirmatory and novel findings

The results of this thesis partly confirm those of previous studies. Especially the conclusion that oral health is worse in PD patients than in controls can be supported by our own findings (chapters 2)[1]. Also, our finding that subjective salivation problems, especially drooling, are highly prevalent in PD patients is a confirmation of previous research (chapter 3)[2,3]. In addition, we confirm that OHRQoL is worse in PD patients, and extended this observation specifically to a Dutch population (chapter 4)[4]. Not surprisingly, older PD patients appear to have an even worse OHRQoL than younger PD patients, wich is a novel observation (chapter 4). Other novel findings are reported in this part of the thesis as well. Notably, our systematic assessment of the literature suggests an association between disease-related factors and oral health in PD patients, which has not been reported before (chapter 2). In addition, there is the novel, yet seemingly contradictory, finding of the common presence of objectively established hyposalivation in PD patients who commonly report drooling subjectively (chapter 3). This is of the utmost importance, because treatments to reduce complaints of drooling are often started by the treating physicians, with potentially negative consequences (viz., dry mouth) for the oral health of PD patients and, hence, their OHRQoL (chapter 3)[5]. Lastly, we identified a widely experienced need to support dental practitioners in the treatment, organisation, education and research related to this special needs group of patients (chapter 5). In summary, oral health is worse and oral diseases are more prevalent in PD patients than in healthy controls, which negatively influences their OHRQoL[6]. Furthermore, our oral health care system currently does not sufficiently support dental practitioners working with PD patients.

Orofacial pain and dysfunction: confirmatory and novel findings

It has been hypothesized that orofacial pain and dysfunction are more prevalent in PD patients than in healthy controls. This hypothesis is based, amongst others, on the observation that bruxism is regulated centrally, whereby the dopaminergic system plays an important role[7]. Furthermore, an increased number of D2 receptors and a reduced D1/D2 ratio have been found in orofacial pain patients, which suggests that the dopaminergic system may influence bruxism behaviour and chronic orofacial pain[8]. However, until recently, orofacial pain and dysfunction were studied insufficiently. In this part of the thesis, we confirmed the hypothesis that orofacial pain and dysfunction are indeed more prevalent in PD patients than in controls (chapters 6, 7, and 8): the scoping review on this matter (chapter 6) confirmed that pain in the orofacial area was more prevalent, that mandibular excursions were limited and movements were slower, and that chewing performance was impaired. In addition, as reported previously in the literature, we found that PD patients experience higher pain intensities than healthy controls[9-11]. However, we are the first to report this specifically in relation to the orofacial area (chapter 7). Similarly, bruxism was also found to be more prevalent in PD patients than in controls (chapter 8). Interestingly, especially awake bruxism appears to be highly prevalent in PD patients (chapter 8), which contrasts with the existing literature on this topic in otherwise healthy individuals[12-14]. To summarise, orofacial pain and dysfunction, including (in particular awake) bruxism, are more prevalent in PD patients than in healthy controls.

Remaining gaps and newly raised questions

After writing this thesis, several knowledge gaps remain, and new questions were raised regarding the umbrella term "oral health" in PD patients. First, the findings in both parts of this thesis, 'oral health and diseases' and 'orofacial pain and dysfunction', emphasize the importance of knowing more about the association of disease-related factors with the various conditions (viz., oral health and diseases, and orofacial pain and dysfunction). Second, the etiological mechanisms of worse oral health and more prevalent orofacial pain and dysfunction in PD patients have not been unravelled yet, although some hypotheses could be formulated. For example, we suggested that difficulties with self-care, higher doses of medication, more hyposalivation problems, and postponing dental visits all negatively influence the oral health of PD patients (chapter 2,3, and 5). In addition, we believe that altered pain processing due to degeneration of specific brain areas, as well as the dosage of dopaminergic medication can negatively influence orofacial pain (chapters 7,8, and 9). Increased insight into the etiological mechanisms involved in PD patients' salivation problems may help to answer the question if, and why a PD patient may report drooling while his/her objective salivary flow rates are low (chapter 3). Additionally, it would be helpful to determine to what extent these seemingly contradictory objective and subjective salivation phenomena coincide, which might allow targeted, personalized treatments. Third, we concluded that OHRQoL is lower in PD patients than in healthy controls, which raises the question whether oral health has a major impact on the general quality of life or whether oral health issues are subordinate to other disease-related symptoms (chapter 4). Fourth, since the interviewed dentists in the qualitative study of chapter 5 report that PD patients experience barriers when seeking help to improve their oral health, an important next step is to identify and analyse which specific barriers are actually present from the patients' perspective

in order to be able to assist PD patients in receiving appropriate dental care from well-educated and trained professionals. Fifth, more insight into the implications of increasing doses of medication and motor and non-motor disease progression on oral health, could help in the development of disease-stage specific preventive measures and treatment strategies in PD patients. Sixth and lastly, it is essential to explore how interdisciplinary collaboration can be enhanced to improve the oral health of PD patients. Clearly, many knowledge gaps remain and novel questions have been raised that should (and can) be addressed in future studies.

Implications

The direct practical implications of this thesis can be divided into three topics that surround the oral health care for PD patients, namely clinical practice, research and education, with the overarching strategical need for interdisciplinary collaboration[15].

In clinical practice, a multidisciplinary approach (e.g., dental and medical practitioners, speech therapists, physiotherapists) to the manifold oral health conditions in PD patients is preferred, even though this is challenging, both within the field of dentistry as well as between medicine and dentistry. Without interdisciplinary collaboration, professionals may even counteract each other's treatments, as suggested in chapter 3. For example, medical practitioners may try to help improve subjective drooling complaints in PD patients by strategies that reduce the production of saliva, and in this way jeopardise oral health since objectively a dry mouth is present[5]. This may happen when the etiological factors of the oral moistening disorders are not exhaustively researched in the individual patient, and patients are not referred to a specialist who is knowledgeable and skilled in this area of expertise. Although this example could be perceived as a critical comment aimed at medical practitioners, actually it is not. On the contrary, most articles included in this thesis are published in dental journals with dental practitioners as their main readership. Hence, it seems that medical practitioners are not adequately informed about the developments in oral health care. Therefore, if we wish to stimulate interdisciplinary work, dental researchers should strive to publish their work in medical journals as well. In this way, the various fields of expertise (viz., dentistry, medicine, and paramedics) can truly intertwine.

To really foster interdisciplinary collaboration, we have to start at the basics, i.e., by learning to speak and understand the same professional language, and perhaps even by being jointly educated. The following example may illustrate this statement. While preparing our protocol paper (chapter 9), one of the reviewers suggested that the different motor symptoms and behaviours that were part of the study protocol (viz., dyskinesia, dystonia, tremor, and bruxism) share a number of characteristics. However, no elaboration of this reviewer's suggestion has been published so far. Therefore, when dental and medical practitioners discuss these motor symptoms and behaviours, a Babylonian confusion is likely to occur as a result. Contributing to the confusion is the fact that the highly-cited international consensus definitions of sleep and awake bruxism are not as inclusive as they should be[16,17]: in order to collaborate with specialists who are more familiar with the treatment of individuals suffering from chronic health problems than dental practitioners, we should not restrict

the definitions of sleep and awake bruxism to 'otherwise healthy individuals' as per the most recent bruxism definitions[17].

Several barriers of delivering oral care to PD patients (e.g., limited knowledge, time constraints, and financial barriers; chapter 5) have been identified[18]. Therefore, an important question to be answered is: how can we overcome these barriers? As published earlier this year, a vision article about dentists and physicians working side-by-side suggests the solution of realizing a substantial overlap between the curricula of dentistry and medicine worldwide[15]. As such, collaboration will naturally arise when we grow up together during education[19], and the threshold of barriers may be lowered. Although this is the most obvious solution to stimulate collaboration between health care practitioners with backgrounds in medicine and dentistry, we are aware that this represents a radical change that might yield discomfort and resistance. A more easily achievable modification would be to include a comprehensive dentistry program in the current study of medicine, and vice versa. In addition, reinforcement of post-initial dental programs and refresher courses for (oral) health care practitioners, including paramedics, can improve the level of knowledge regarding (oral) health in its broadest sense, so that every (oral) health care practitioner surrounding the PD patient is up-to-date.

In short, interdisciplinary collaboration could be stimulated step-by-step, however, the best-possible situation can only be achieved when we are willing to approach the obstacles from the very beginning by means of creating a common professional language and a substantial overlap between dental and medical education.

Conclusion

Oral health in its broadest sense is worse in PD patients than in healthy controls. When improving oral health care in this vulnerable patient group is deemed desirable by all stakeholders, we must acknowledge the difficulties experienced by the (oral) health care practitioners working with these patients to establish a well-oiled interdisciplinary collaboration.

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Chapter 11

Summary

Summary

The general aim of this thesis was to further our knowledge on the umbrella term “oral health” in patients with Parkinson’s Disease (PD), including oral hygiene, oral health and diseases (e.g., gingivitis, periodontitis, tooth decay, and tooth loss) and orofacial pain and dysfunction (e.g., temporomandibular disorders (TMD) pain, limited jaw movements, and bruxism). The thesis is divided into two parts: (i) oral health and diseases in PD patients (Chapters 2-5) and (ii) orofacial pain and dysfunction in PD patients (Chapters 6-9). In this chapter, a summary of the thesis is given.

Part 1: Oral health and diseases

In **chapter 2**, we aimed to provide a comprehensive review of the available literature on oral health in PD and to evaluate factors associated with oral health problems. In total, 41 studies were included. Most studies indicated that oral health is worse in PD patients than in healthy controls. Only the prevalence of being edentulous or wearing complete dentures did not differ between PD patients and controls. The 13 studies that analysed factors associated with oral health problems in PD showed that gender, disease duration and severity, and medication usage could be associated with worse oral health in PD patients. Concluding, we found that oral health of PD patients was worse than that of healthy controls, and that this is suggested to be associated with the duration and severity of PD and medication usage. Therefore, we advised regular appointments with oral health care professionals, with an important focus on prevention.

Because salivation may be of influence on the findings above, salivation problems in PD patients were analysed employing a systematic and critical overview of the literature, as presented in **chapter 3**. Both salivary flow rate and subjectively experienced xerostomia and drooling in patients with PD were analysed. Furthermore, in this chapter, we aimed to discuss the potential aetiological pathways for all types of salivation problems. In total, 63 studies were included. The presence of xerostomia in patients with PD ranged from 49% to 77%, and that of drooling from 5% to 80%. When patients with PD reported their experiences concerning salivation problems, either xerostomia (7 studies) or drooling (14 studies) were found to be more common than in controls. In 7 articles, a lower unstimulated salivary flow was found, and in 3 articles, a lower stimulated salivary flow was observed in PD patients than in a control group. None of the articles with both a control group and a patient group reported a higher salivary flow in patients with PD. Although some of these findings appeared contradictory, the mechanisms involved in xerostomia and drooling complaints are likely not the same. Also, there was a lack of studies combining objective measurements and subjective complaints. Therefore, it was impossible to determine to what extent these phenomena were present in the same individual. In this chapter, we concluded that that the complexity of salivation problems present in PD patients necessitates a multidisciplinary approach in order to avoid mutually counteracting treatments from different healthcare professionals.

Both worse oral health and salivation problems can influence the oral health-related quality of life (OHRQoL) of PD patients. When the oral health status is reduced, this may lead to additional problems, such as difficulties with chewing, which may, in turn, be associated with weight loss that

already is a problem in some PD patients. Additionally, it has been suggested that chewing problems may be associated with cognitive decline, which is one of the non-motor symptoms that PD patients may experience. In a population that is already in need of help provided by different healthcare providers, the consequences of worsening oral health could thus further increase the pressure on our health care system. Therefore, the study described in **chapter 4** was performed to evaluate whether the OHRQoL of patients with PD is worse compared to that of healthy controls, in a Dutch population. In addition, we aimed to identify factors associated with the OHRQoL of patients with PD. In our study, PD patients showed a lower OHRQoL than healthy controls. Furthermore, disease-related and oral health-related variables were positively (i.e., being dentate) and negatively (i.e., motor aspects of experiences of daily living, worsening of the oral environment during the disease course, having tooth wear, and possibly burning mouth syndrome) associated with OHRQoL. Although problems concerning oral health are probably subordinate to other problems present in PD patients, the findings in this chapter suggested that the OHRQoL may be impaired in patients with PD. By being aware of this, dentists can be more alert and thus improve PD patients' oral health to prevent further deterioration of their OHRQoL.

Because it is essential to prevent worsening oral health for both OHRQoL and general health in an already vulnerable population, the study described in **chapter 5** was performed to gain a deeper understanding of the experiences of dental practitioners regarding treatment (viz., measures and prevention), organization (viz., politics, rules and regulations, accessibility and initiatives), and education and research, including competence, related to the oral health of patients with PD. With more knowledge regarding the views of dentists treating these patients, gaps were identified based on which suitable solutions may be found in the future. The interviewees highlighted deficiencies in the Dutch oral health care system regarding treatment, organization, education and research concerning oral health care for PD patients. Mainly, education was lacking since this topic is not well-represented in the current dental curriculum, if at all. In addition, dentists' knowledge regarding oral health in older individuals was experienced as limited. Although less bureaucracy and more interdisciplinary approaches were suggested to improve oral health care in PD patients, these issues represent major societal, political, and educational challenges. Furthermore, more and higher-quality research regarding oral health in PD patients is needed to close the knowledge gap and ease the uncertainty of dental practitioners.

Part 2: Orofacial pain and dysfunction

In **chapter 6**, a broad overview of the relevant literature was written on the prevalence of orofacial pain and dysfunction in patients with PD, and comparisons with otherwise healthy controls were made when available. Furthermore, we aimed to see which patient-related characteristics were associated with orofacial pain and/or dysfunction in PD patients, and we generated hypotheses for future research on this topic. Most included studies showed that orofacial pain and dysfunction in the orofacial area were more common in PD patients than in healthy controls. Moreover, some studies found a correlation between, on the one hand, disease severity and other disease-related factors (e.g., medication usage) and, on the other hand, orofacial pain and/or dysfunction. Based

on our findings, several hypotheses were formulated: (i) orofacial pain and dysfunction are more prevalent in PD patients than in healthy controls; (ii) disease duration and severity are associated with a higher prevalence of orofacial pain and worse orofacial function in patients with PD as compared to healthy controls; and (iii) medication, for example, dopaminergic therapy, reduces the prevalence of pain, raises pain thresholds, and improves orofacial dysfunction in patients with PD. To test these hypotheses, in this chapter, recommendations were given for designing a study that includes PD patients with a wide range of disease stages, from disease onset to advanced stages, in order to study whether disease duration and severity are associated with more orofacial pain and worse orofacial function. In addition, disease-related factors (e.g., dose of dopaminergic medication) were recommended to be included in future studies as to establish whether or not these factors can influence orofacial pain and/or dysfunction in PD patients. Furthermore, using validated and internationally approved diagnostic criteria (e.g., for TMD diagnosis, the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD)) was highly recommended as to be able to, for example, compare the results of different studies. Finally, an interdisciplinary approach was recommended to overcome bias related to the field of interest. Ultimately, this could contribute to improved, individualised, and preferably preventive strategies to reduce orofacial pain, dysfunction, and its consequences in PD patients.

The aim of **chapter 7** was to gain more insight into a possible association between bruxism and orofacial pain or TMD pain on the one hand and PD and parkinsonism (PR) on the other. The results showed a significant association between both circadian manifestations of bruxism (viz., possible sleep and awake bruxism) and PD/PR. Moreover, a significant association of orofacial pain and TMD pain was found with and PD/PR. The study population of chapter 7 was broad and also included PR patients. Therefore, in **chapter 8,** we focused only on the PD patients ***t***o determine the prevalence of possible awake and sleep bruxism in that specific patient population. The results showed a respective prevalence of 46.0% and 24.3% for these conditions. Furthermore, the aim was to investigate possible associations between the dose of dopaminergic medication and the presence of awake and sleep bruxism. The results showed that in a PD population, the Levodopa Equivalent Daily Dosage (LEDD) was not associated with the self-reports of awake and sleep bruxism. Furthermore, this study examined whether other factors were significantly associated with self-reported awake and sleep bruxism. Co-occurrence of both awake bruxism and sleep bruxism was observed. In addition, there was an association between tooth wear and both circadian bruxism manifestations. Finally, awake bruxism was also found to be associated with TMD pain. In this chapter, the clinical implications were that (oral) health care providers should be aware of the possibility of sleep and awake bruxism activity in PD patients, along with the negative health outcomes these activities may have (viz., TMD pain, tooth wear).

To overcome the limitations of **chapter 7** and **chapter 8**, and to proceed with the suggestions made in **chapter 6**, a clinical study protocol was presented in **chapter 9**. The primary aim of this protocol is to objectively measure the presence of bruxism and TMD pain in a population of patients with PD. Furthermore, the three secondary aims of the protocol are described as follows: (i) to identify which

factors are associated with bruxism and TMD pain in PD patients, (ii) to investigate whether the salivary flow, the pH, and the buffer capacity of saliva in patients with PD are related to the severity of tooth wear, and (iii) to investigate with Dopamine Transporter - Single Photon Emission Computed Tomography' (DAT-SPECT) whether there is a relationship between the degree of presynaptic dopaminergic loss and the presence of bruxism in these patients. Upon completion, this study will give more detailed information about the presence of bruxism and TMD pain in patients with PD, as well as possible associated factors like medication usage and severity of the disease. Also, more clinically relevant information will become available for dentists and other oral health care professionals about the amount of tooth wear and the composition of saliva in patients with PD.

Finally, **chapter 10** discussed this thesis' confirmatory and novel findings. Furthermore, we identified remaining knowledge gaps and newly raised questions related to the oral health of PD patients. Moreover, the clinical, research, and educational implications of this thesis' findings were outlined.

Based on the outcomes of the studies included in this thesis, it can be concluded that oral health in its broadest sense is worse in PD patients than in healthy controls. When improving oral health care in this vulnerable patient group is deemed desirable by all stakeholders, we must acknowledge the difficulties experienced by the (oral) health practitioners working with these patients to establish a well-oiled interdisciplinary collaboration.

Chapter 12

Samenvatting

Samenvatting

Het algemene doel van dit proefschrift was het vergroten van onze kennis over mond-gezondheid bij patiënten met de ziekte van Parkinson (ZvP), waaronder mondhygiëne, mondziekten (bijv. gingivitis, parodontitis, tandbederf en verlies van gebitselementen) en orofaciale pijn en disfunctie (bijv. temporomandibulaire disfunctie (TMD)-pijn, beperkte kaakbewegingen en bruxisme). Het proefschrift is opgedeeld in twee delen: (i) mondgezondheid en mondziekten bij patiënten met de ZvP (hoofdstukken 2-5) en (ii) orofaciale pijn en disfunctie bij patiënten met de ZvP (hoofdstukken 6-9). In dit hoofdstuk wordt een samenvatting van het proefschrift gegeven.

Deel 1: Mondgezondheid en mondziekten

Hoofdstuk 2 geeft een uitgebreid overzicht van de beschikbare literatuur over mondgezondheid bij de ZvP waarbij factoren worden geëvalueerd die verband houden met mondgezondheidsproblemen. In totaal werden 41 studies geïncludeerd. De meeste onderzoeken gaven aan dat de mondgezondheid bij patiënten met de ZvP slechter is dan bij gezonde controles. Alleen de prevalentie van tandenloosheid en het dragen van een volledige prothese verschilde niet tussen patiënten met de ZvP en controles. De 13 onderzoeken waarin factoren werden geanalyseerd die verband houden met mondgezondheidsproblemen bij de ZvP toonden aan dat geslacht, ziekteduur en -ernst, en medicatiegebruik geassocieerd kunnen zijn met een slechtere mondgezondheid bij patiënten met de ZvP. Concluderend vonden we dat de mondgezondheid van patiënten met de ZvP slechter was dan die van gezonde controles, en dat dit verband kan houden met de duur en ernst van de ZvP en het medicatiegebruik. Daarom adviseerden wij regelmatige afspraken met mondzorgprofessionals, met een belangrijke focus op preventie.

Omdat speeksel van invloed kan zijn op bovenstaande bevindingen, werden speekselproblemen bij patiënten met de ZvP geanalyseerd met behulp van een systematisch en kritisch overzicht van de literatuur, zoals gepresenteerd in **hoofdstuk 3**. Zowel de speekselvloed als het subjectief ervaren van xerostomie (droge mond) en kwijlen bij patiënten met de ZvP werden geanalyseerd. Verder wilden we in dit hoofdstuk de mogelijke etiologische factoren voor alle soorten speekselproblemen bespreken. In totaal werden 63 onderzoeken geïncludeerd. De aanwezigheid van xerostomie bij patiënten met de ZvP varieerde van 49% tot 77%; die van kwijlen van 5% tot 80%. Wanneer patiënten met de ZvP hun ervaringen met speekselproblemen rapporteerden, bleek xerostomie (7 onderzoeken) of kwijlen (14 onderzoeken) vaker voor te komen dan bij controles. In 7 artikelen werd een lagere ongestimuleerde speekselvloed gevonden en in 3 artikelen werd een lagere gestimuleerde speekselvloed waargenomen bij patiënten met de ZvP dan in een controlegroep. Ondanks dat patiënten met de ZvP meer kwijlden, rapporteerde geen van de artikelen met zowel een controlegroep als een patiëntengroep een hogere speekselvloed bij patiënten met de ZvP. Hoewel sommige van deze bevindingen tegenstrijdig leken, zijn de mechanismen die betrokken zijn bij xerostomie en kwijlen waarschijnlijk niet hetzelfde. Ook ontbrak het aan studies waarin objectieve metingen en subjectieve klachten werden gecombineerd. Daarom was het onmogelijk om vast te stellen in hoeverre deze verschijnselen bij hetzelfde individu aanwezig waren. In dit

hoofdstuk hebben we geconcludeerd dat de complexiteit van speekselproblemen bij patiënten met de ZvP een multidisciplinaire aanpak vereist om te voorkomen dat behandelingen van verschillende zorgverleners elkaar tegenwerken.

Zowel een slechtere mondgezondheid als speekselproblemen kunnen de mondgezondheids-gerelateerde kwaliteit van leven ('oral health-related quality of life' (OHRQoL)) van patiënten met de ZvP beïnvloeden. Wanneer de mondgezondheidsstatus wordt verminderd, kunnen andere problemen optreden, zoals moeilijkheden bij het kauwen, die op hun beurt kunnen worden geassocieerd met bijvoorbeeld gewichtsverlies. Dit laatste is een veelvoorkomend probleem bij mensen met de ZvP, en kauwproblemen kunnen dit verergeren. Daarnaast wordt er gesuggereerd dat kauwproblemen geassocieerd zijn met cognitieve achteruitgang, wat op zijn beurt ook een van de niet-motorische symptomen is die patiënten met de ZvP kunnen ervaren. In een populatie die al hulp nodig heeft van verschillende zorgverleners, kunnen de gevolgen van een verslechtering van de mondgezondheid de druk op ons gezondheidszorgsysteem dus verder vergroten. Daarom werd de studie beschreven in **hoofdstuk 4** uitgevoerd, waarbij geëvalueerd werd of de OHRQoL van patiënten met de ZvP slechter was in vergelijking met die van gezonde controles, in een Nederlandse populatie. Daarnaast wilden we factoren identificeren die verband houden met de OHRQoL van patiënten met de ZvP. In onze studie vertoonden patiënten met de ZvP een slechtere OHRQoL dan gezonde controles. Bovendien waren ziekte-gerelateerde en mondgezondheidsgerelateerde variabelen positief (d.w.z. betand zijn) en negatief (d.w.z. motorische aspecten van ervaringen in het dagelijks leven, verslechtering van de mondgezondheid tijdens het ziekteverloop, gebitsslijtage en een mogelijk mondbrandensyndroom) geassocieerd met OHRQoL. Hoewel problemen met betrekking tot mondgezondheid waarschijnlijk ondergeschikt zijn aan andere problemen bij patiënten met de ZvP, suggereerde dit hoofdstuk dat de OHRQoL bij patiënten met de ZvP verminderd is. Door zich hiervan bewust te zijn, kunnen tandartsen alerter zijn en zo de mondgezondheid van patiënten met de ZvP verbeteren om verdere verslechtering van hun OHRQoL te voorkomen.

Omdat het essentieel is om een slechtere mondgezondheid (voor zowel de OHRQoL als de algemene gezondheid) in een toch al kwetsbare populatie te voorkomen, is het onderzoek uitgevoerd dat is beschreven in **hoofdstuk 5**. Dit hoofdstuk had als doel om meer inzicht te verkrijgen in de ervaringen van (gespecialiseerde) tandartsen met betrekking tot de behandeling (namelijk maatregelen en preventie), organisatie (namelijk politiek, wet- en regelgeving, toegankelijkheid en initiatieven) en onderwijs en onderzoek, inclusief competentie, van mondzorg bij patiënten met de ZvP. Met meer kennis over de opvattingen van tandartsen die deze patiënten behandelen, werden hiaten geïdentificeerd, op basis waarvan in de toekomst passende oplossingen kunnen worden gevonden. De geïnterviewden wezen op tekortkomingen in het Nederlandse mondzorgsysteem op alle drie de gebieden. Vooral het onderwijs vertoonde gebreken, omdat dit onderwerp niet of niet goed vertegenwoordigd is in het huidige tandheelkundige curriculum. Daarnaast werd de kennis van tandartsen over mondgezondheid bij ouderen als beperkt ervaren. Hoewel minder bureaucratie en een meer interdisciplinaire benadering werden voorgesteld om de mondgezondheid van patiënten met de ZvP te verbeteren, stelt het behalen van deze doelen ons voor grote maatschappelijke,

politieke en educatieve uitdagingen. Verder is er meer en kwalitatief beter onderzoek naar de mondgezondheid van patiënten met de ZvP nodig om de kennisklоof te dichten en de onzekerheid van algemene en gespecialiseerde tandartsen te verminderen.

Deel 2: Orofaciale pijn en disfunctie

In **hoofdstuk 6** is een overzicht van de relevante literatuur over de prevalentie van orofaciale pijn en disfunctie bij patiënten met de ZvP, en werden vergelijkingen gemaakt met gezonde controlepersonen (indien beschikbaar). Verder onderzochten we welke patiëntgerelateerde kenmerken geassocieerd waren met orofaciale pijn en/of disfunctie bij patiënten met de ZvP, en hebben we hypothesen geformuleerd voor toekomstig onderzoek over dit onderwerp. De meeste onderzoeken toonden aan dat orofaciale pijn en disfunctie vaker voorkwamen bij patiënten met de ZvP dan bij gezonde controles. Bovendien vonden sommige onderzoeken een verband tussen enerzijds de ernst van de ziekte en andere ziektegerelateerde factoren (bijvoorbeeld medicatiegebruik) en anderzijds orofaciale pijn en/of disfunctie. Op basis van onze bevindingen werden verschillende hypothesen geformuleerd: (i) orofaciale pijn en disfunctie komen vaker voor bij patiënten met de ZvP dan bij controles; (ii) ziekteduur en -ernst zijn geassocieerd met een hogere prevalentie van orofaciale pijn en slechtere orofaciale functie bij patiënten met de ZvP in vergelijking met controles; en (iii) medicatie, bijvoorbeeld dopaminerge therapie, vermindert de prevalentie van pijn, verhoogt pijndrempels en verbetert orofaciale disfunctie bij patiënten met de ZvP. In dit hoofdstuk werden aanbevelingen gedaan voor het opzetten van een studie met patiënten met de ZvP met een breed scala aan ziektestadia, van het begin van de ziekte tot de gevorderde stadia, om te onderzoeken of de duur en ernst van de ziekte geassocieerd zijn met meer orofaciale pijn en een slechtere orofaciale functie. Bovendien werd aanbevolen om ziektegerelateerde factoren (bijv. de dosis van dopaminerge medicatie) op te nemen in toekomstige studies om vast te stellen of deze factoren orofaciale pijn en/of disfunctie bij patiënten met de ZvP kunnen beïnvloeden. Verder werd het gebruik van gevalideerde en internationaal goedgekeurde diagnostische criteria (bijv. de “Diagnostic Criteria for Temporomandibular Disorders” (DC/TMD) voor een TMD-diagnose) sterk aanbevolen om bijvoorbeeld de resultaten van verschillende onderzoeken te kunnen vergelijken. Ten slotte werd een interdisciplinaire benadering aanbevolen om bias met betrekking tot het interessegebied te overwinnen. Uiteindelijk zou dit kunnen bijdragen aan verbeterde, geïndividualiseerde en bij voorkeur preventieve strategieën om orofaciale pijn, disfunctie en de gevolgen daarvan bij patiënten met de ZvP te verminderen.

Het doel van **hoofdstuk 7** was om meer inzicht te krijgen in het mogelijke verband tussen bruxisme en orofaciale pijn of TMD-pijn enerzijds en de ZvP en parkinsonisme (PR) anderzijds. De resultaten lieten een significant verband zien tussen zowel beide circadiane manifestaties van bruxisme (d.w.z. mogelijk slaap- en waakbruxisme) en de ZvP/PR. Bovendien werd een significante associatie gevonden tussen zelfgerapporteerde orofaciale pijn en TMD-pijn enerzijds, en de ZvP/PR anderzijds. Omdat de onderzoekspopulatie van **hoofdstuk 7** breed was en ook PR-patiënten omvatte, hebben we ons in **hoofdstuk 8** alleen gericht op de patiënten met de ZvP om de prevalentie van mogelijk waak- en slaapbruxisme in deze specifieke patiëntenpopulatie te bepalen. De resultaten toonden

een respectievelijke prevalentie van 46.0% en 24.3% voor deze aandoeningen. Verder was het doel om mogelijke associaties te onderzoeken tussen de dosis van de dopaminerge medicatie en de aanwezigheid van waak- en slaapbruxisme. De resultaten toonden aan dat in een populatie van patiënten met de ZvP, de dagelijkse dosering van dopaminerge medicatie ('Levodopa Equivalent Daily Dosage' (LEDD)) niet geassocieerd was met de zelfrapportage van waak- en slaapbruxisme. Ook werd in deze studie onderzocht of andere factoren significant geassocieerd waren met zelfgerapporteerde waak- en slaapbruxisme. Het gelijktijdig optreden van zowel waakbruxisme als slaapbruxisme werd waargenomen. Bovendien was er een verband tussen gebitsslijtage en beide circadiane bruxisme-manifestaties. Ten slotte bleek waakbruxisme geassocieerd te zijn met zelfgerapporteerde TMD-pijn. In dit hoofdstuk waren de klinische implicaties dat (mond) zorgverleners moeten worden gewaarschuwd voor de mogelijkheid van slaap- en waakbruxisme-activiteiten bij patiënten met de ZvP, en tevens voor de mogelijke negatieve gezondheidsresultaten van deze activiteiten (namelijk TMD-pijn, gebitsslijtage).

Om de beperkingen van **hoofdstuk 7** en **hoofdstuk 8** te overwinnen en voort te borduren op de suggesties in **hoofdstuk 6**, werd in **hoofdstuk 9** een klinisch onderzoeksprotocol gepresenteerd. Het primaire doel van dit protocol is om de aanwezigheid van bruxisme en TMD-pijn objectief te meten in een populatie van patiënten met de ZvP. Verder worden de drie secundaire doelstellingen van het protocol als volgt beschreven: (i) identificeren welke factoren geassocieerd zijn met bruxisme en TMD-pijn bij patiënten met de ZvP, (ii) onderzoeken of de speekselvloed, de pH en de buffercapaciteit van speeksel bij patiënten met de ZvP gerelateerd zijn aan de ernst van gebitsslijtage, en (iii) om met een dopamine transporter scan ('Dopamine Transporter - Single Photon Emission Computed Tomography' *(*DaT-SPECT)) te onderzoeken of er een verband is tussen de mate van presynaptisch dopaminerg verlies en de aanwezigheid van bruxisme bij deze patiënten. Concluderend zal deze studie meer gedetailleerde informatie geven over de aanwezigheid van bruxisme en TMD-pijn bij patiënten met de ZvP, evenals mogelijke geassocieerde factoren zoals medicatiegebruik en de ernst van de ziekte. Ook komt er meer klinisch relevante informatie beschikbaar voor tandartsen en andere (mond)zorgprofessionals over de mate van gebitsslijtage en de samenstelling van speeksel bij patiënten met de ZvP.

Ten slotte besprak **hoofdstuk 10** de bevestigende en nieuwe bevindingen van dit proefschrift. Verder identificeerden we de resterende kennislacunes en nieuw opgeworpen vragen met betrekking tot de mondgezondheid van patiënten met de ZvP. Bovendien werden de klinische, onderzoeks- en educatieve implicaties van de bevindingen van dit proefschrift geschetst.

Op basis van de uitkomsten van de onderzoeken die in dit proefschrift zijn opgenomen, kan worden geconcludeerd dat de mondgezondheid in de breedste zin van het woord slechter is bij patiënten met de ZvP dan bij gezonde controlepersonen. Wanneer verbetering van de mondgezondheid bij deze kwetsbare patiëntengroep door alle belanghebbenden wenselijk wordt geacht, zullen we de moeilijkheden die (mond)gezondheidsprofessionals, die met deze patiënten werken, ervaren moeten erkennen om een goed geoliede interdisciplinaire samenwerking tot stand te kunnen brengen.

Authors' contributions

Chapter 2| Parkinson's disease and oral health: a systematic review

Merel C. Verhoeff, Denise Eikenboom, Michail Koutris, Sharine Tambach, Ralph de Vries, Henk W. Berendse, Karin D. van Dijk, Frank Lobbezoo.

MV, MK and FL contributed to the design of this study. RdV performed the search. MV, DE and ST screened the search results. MV and DE extracted the data from papers and DE performed the quality assessment of the included articles. All authors contributed to the clinical perspective and final review of this manuscript.

Chapter 3| Salivation in Parkinson's disease: a scoping review

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MV conceived of the presented idea in consultation with MK and FL. RdV performed the search. MV and MK selected the included articles, with discussion, when necessary, with FL. All authors discussed the results and contributed to the final manuscript.

Chapter 4| Oral health-related quality of life in patients with Parkinson's disease

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All co-authors took part in the conceptualisation and preparation of this manuscript. MV and AvL performed the analysis of data and drafted a first version. AS provided the data for the historical controls. MV, FL, AvL, AS and MK revised the manuscript.

Chapter 5| Clinicians' view on the management of oral health in Parkinson's disease patients: a qualitative study

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MV, MT, and FL developed and designed this study. AB and MH performed and transcribed the interviews. MV, AB, and MH analyzed the interviews and discussed them with MT when applicable. MV drafted this manuscript. Finally, all authors reviewed the manuscript and approved the final version.

Chapter 6| Orofacial pain and dysfunction in patients with Parkinson's disease: a scoping review

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MV, MK and FL conceived of the present idea. RdV performed the search. MV, ST and DE screened the results, and extracted the data from the papers. All authors contributed to the clinical perspective and final review of this manuscript.

Chapter 7| Parkinson's disease, temporomandibular disorders and bruxism: a pilot study

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All authors (MV, FL, PW, GA, MK) were involved in designing this study. MV obtained the approval of

the Medical Ethics Review Committee and drafted the manuscript. Finally, all authors (MV, FL, PW, GA, MK) gave feedback on the draft and approved the final manuscript

Chapter 8| Is dopaminergic medication dose associated with self-reported bruxism in Parkinson's disease? A cross-sectional, questionnaire-based study

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MV, MK and FL contributed to the study conception and design. Data collection took place by MV. Material preparation was done by MV, MvS, AB, MH and KvD. MV wrote the first draft and supervision was provided by MK, MvS and FL. Finally, all authors edited and finalized the draft.

Chapter 9| Parkinson's disease, temporomandibular disorder pain and bruxism and its clinical consequences: a protocol of a single-centre observational outpatient study

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All authors (MV, MK, KvD, HB and FL) were involved in designing this study. MV obtained the approval of the Medical Ethics Review Committee and drafted the manuscript. Finally, all authors (MV, MK, KvD, HB and FL) gave feedback on the draft and approved the final manuscript.

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“Have fun, even if it’s not the same kind of fun everyone else is having”

C.S. Lewis