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Parkinson's disease, temporomandibular disorder pain, and bruxism and its clinical consequences. A protocol of a clinical 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 could negatively influence patients' satisfaction and quality of life. The present study is designed to clinically and more objectively investigate the prevalence of bruxism and TMD pain in PD patients. The secondary aim of the study is to identify factors associated with the presence of 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 clinical 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 the 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.
Trial registration: NL8307
Keywords: Parkinson's Disease; Bruxism; Temporomandibular Disorders; Protocol; Tooth wear; Saliva

Strengths and limitations of this study:

- This clinical study will provide accurate data on the prevalence of bruxism and painful temporomandibular disorders in Parkinson patients attending the outpatient clinic for movement disorders of Amsterdam UMC, location VUmc, and their possible associated factors like medication usage and disease severity.
- Novel information about tooth wear and saliva composition and quantity in patients with Parkinson's disease will be collected.

- Since polysomnographic recordings for the assessment of definite sleep bruxism are not feasible in this study, a portable, single-channel electromyographic recorder is used instead.
- Electromyographic recordings will be performed for several nights in a row, thus taking into account the fluctuating nature of sleep bruxism.
- Because of the design of this study, no causal relationships can be established between the outcome variables and predictors.

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 pain, anxiety, depression, sleep problems, and cognitive dysfunction[3,4]. 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 therefore may occur more frequently[5]. Dentists regularly see patients with movement disorders in the orofacial area. The most common oral movement disorder in the dental office is bruxism, which 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"[6]. It can occur during sleep, indicated as sleep bruxism, or during wakefulness, indicated as awake bruxism[6]. 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[7]. TMD can present as painful and non-painful conditions. Patients with TMD can report, for example, pain (including headache), limitations in the movement of the mandible, and joint noises[7]. Both tooth wear and TMD may affect the oral health-related quality of life[8].

In a population with PD patients, oral health was recently studied[9]. It was shown that the oral health in PD patients is deteriorated as compared to their peers without PD. Besides, medication use can influence salivation production, and in turn the oral environment[10]. Also, gastrointestinal problems are more frequently shown in patients with PD. In turn, this could influence the presence of tooth wear due to reflux[11,12].

While oral health care in PD has not been studied widely[9], 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 a condition that is considered to be regulated centrally and not peripherally[13]. Also, in the pathophysiology of both PD and bruxism, the brain dopamine system plays an important role [14–16]. Besides, sleep disturbances[17] that are present both in PD[18] and in sleep bruxism, are associated with arousal activity[17,18]. As a result of such arousal activity, sleep bruxism may occur more frequently in people with sleep disturbances than in those without[19]. 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[20]. This is a characteristic that is also seen in sleep bruxism patients[21]. Furthermore, bruxism is considered as a risk factor for TMD[22]. 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[3,23]. Finally, suggestions have been put forward that alterations in the dopaminergic system are also present in patients with pain in the orofacial region[24], 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[25]. Also, PD patients reported a higher mean TMD-pain intensity than controls [25]. However, since this was a questionnaire-based study, extrapolation of these findings requires further verification through clinical data. To overcome some of the limitations of the previous pilot study, the present protocol was designed. The planned study will acquire more objective clinical/instrumental measures for awake and sleep bruxism and TMD pain, which can give more valid information on outcomes like the prevalence of bruxism in this population. Also, additional factors, such as the severity of PD and cognitive function, will be included as possible predictors for the presence of 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 prevalence of bruxism and TMD pain in PD patients, through objective measurements. Based on our pilot-study outcomes[25], we hypothesise that the prevalence of bruxism and TMD pain in the current population will be higher than in their peers without PD, described in the literature[26,27].

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

1. To identify which factors are associated with the presence of bruxism and TMD pain in PD patients. We hypothesise that factors like medication usage[14], disease severity[13,15], psychosocial factors[28–30], and lifestyle factors[28,29,31] 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[12].
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 clinical 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.

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 ≥ 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 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)[32]. For the assessment of awake bruxism, patients will use, for 5 complete registration days, the BruxApp[33], which is a mobile application for the recording of bruxism activity based on ecological momentary assessment[6]. According to international consensus, a classification of the probability that bruxism is present can be made as follows: possible, probable, and definite bruxism presence[6]. 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)[6].

The TMD-pain diagnosis will be established according to the Diagnostic Criteria for TMD (DC/TMD)[34], 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[34].

Secondary study parameters

To identify which factors are associated with the presence of 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). Most of these variables have already been reported as risk factors for bruxism[29] and/or TMD[35] in the general population[28–30]. 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. Finally, if DAT-SPECT imaging is available, we will compare the measured presynaptic striatal dopaminergic deficit between participants with and without bruxism[36].

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[21]. Taking the cautious approach, we calculated the sample size for all conditions and chose the largest sample size. Aiming for a precision of 5% with a level of confidence of 95%, 382 participants are needed[37]. 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 the presence of 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 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 and analysed using the independent sample t-test[36,38].

Patient and public involvement

Neither patients nor the community were involved in the design or performance of this study. However, feedback from participants of the earlier pilot study[21] was used to design this 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 prevalence 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 the presence of 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 prevalence 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[21,39]. Furthermore, 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[6]. In addition, the clinical examination according to the DC/TMD[34] enables setting a valid TMD-pain diagnosis, making a distinction between several TMD complaints, and comparing the outcomes with other (inter-) national research.

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[40,41], 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[6]. 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[32]. 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[43]. This is an important issue, because such movement disorders can be present in patients with PD related to their medication usage. Fortunately, in the questionnaire and clinical examination of the MDS-UPDRS[44] (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.

In conclusion, this study will give more detailed information about the prevalence 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.

Ethics and dissemination:

This study protocol has been approved by the Medical Ethics Review Committee of Amsterdam UMC, location VUmc; NL. 2019.143). Informed consent will be obtained from all participants. A data monitor will meet annually to primarily concentrate on the safety of patients, and will be monitoring the collected data and informed consents.

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.

Authors contribution

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

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Competing interest

Dr. Lobbezoo reports grants and other from Sunstar Suisse SA, grants from Somnomed-Goedegebuure, grants from Airway Management, grants from Vivisol, grants from Health Holland, outside the submitted work.

Tables

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)[45]	**2**. for using the GrindCare: pacemaker
3. fulfil clinical diagnostic criteria for PD[46]	**3.** for using the BruxApp: no smartphone

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)[45];(Parkinson's Disease Cognitive Functional Rating Scale, PD-CFRS)[42]**
2.	**Disease stage (Hoehn & Yahr)[47]; Disease severity (Unified Parkinson's Disease Rating Scale – III, UPDRS-III)[44]**
3.	**Dopaminergic medication (Levodopa equivalent daily dose, LEDD)[48]**
4.	**Neuropsychiatric symptoms: Depression (Beck Depression Inventory-ii, BDI-ii)[49]; Apathy (Apathy evaluation scale, AES)[50]; Anxiety (Parkinson Anxiety Scale, PAS)[51]; Psychotic (Parkinson's Disease-adapted scale for assessment of positive symptoms, SAPS-PD)[52]; Impulse control (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, QUIP-RS)[53]**
5.	**Presynaptic dopaminergic loss, when applicable (brain imaging) (Dopamine Transporter Single Photon Emmission Computed Tomography, DAT-SPECT)[36,38]**
6.	**Quality of sleep (Scales for Outcomes PD Sleep, SCOPA-SLEEP)[54]**
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)[55]
	2. TMD pain (according to the Diagnostic Criteria for TMD, DC/TMD)[34] and intensity (graded chronic pain scale, GCPS)[56]
	3. Tooth wear
	4. Sleep (Obstructive Sleep Apnea, STOP-Bang NL)[57]
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))[34]
	2. Quantitative tooth wear screening (part of the Tooth Wear Evaluation System, TWES)[58]
	3. A brief screening of the dental prosthesis (when applicable)
	4. Dry mouth screening (Clinical Oral Dryness Score, CODS)[59]
	5. Jaw-mobility examination (DC/TMD)[34]
	6. Joint noises examination (DC/TMD)[34]

	7. Palpation of masticatory muscles and temporomandibular joints (DC/TMD)[34]
	8. Dynamic/static tests [60]
	9. Bruxoprovocationtest [61]
	10. Saliva test (Saliva-Check Buffer®)[62]
Registration	1. BruxApp [61]
	2. GrindCare® GC4[32,63]

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)

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Figure Legends

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 both conditions; 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.*

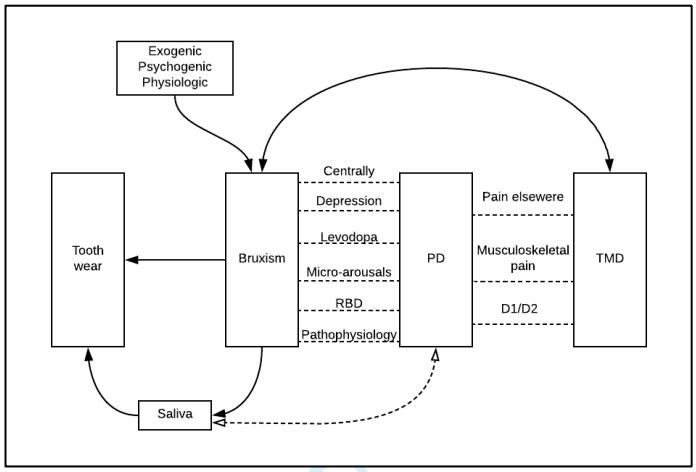

Figure 1. Visualization of the possible interactions between the different research variables. *Parkinson's Disease (PD) is associated with bruxism through different variables: the dopaminergic system (pathophysiology) plays a role in both conditions; the prodromal phase of PD (RBD) shows the same characteristics 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.*

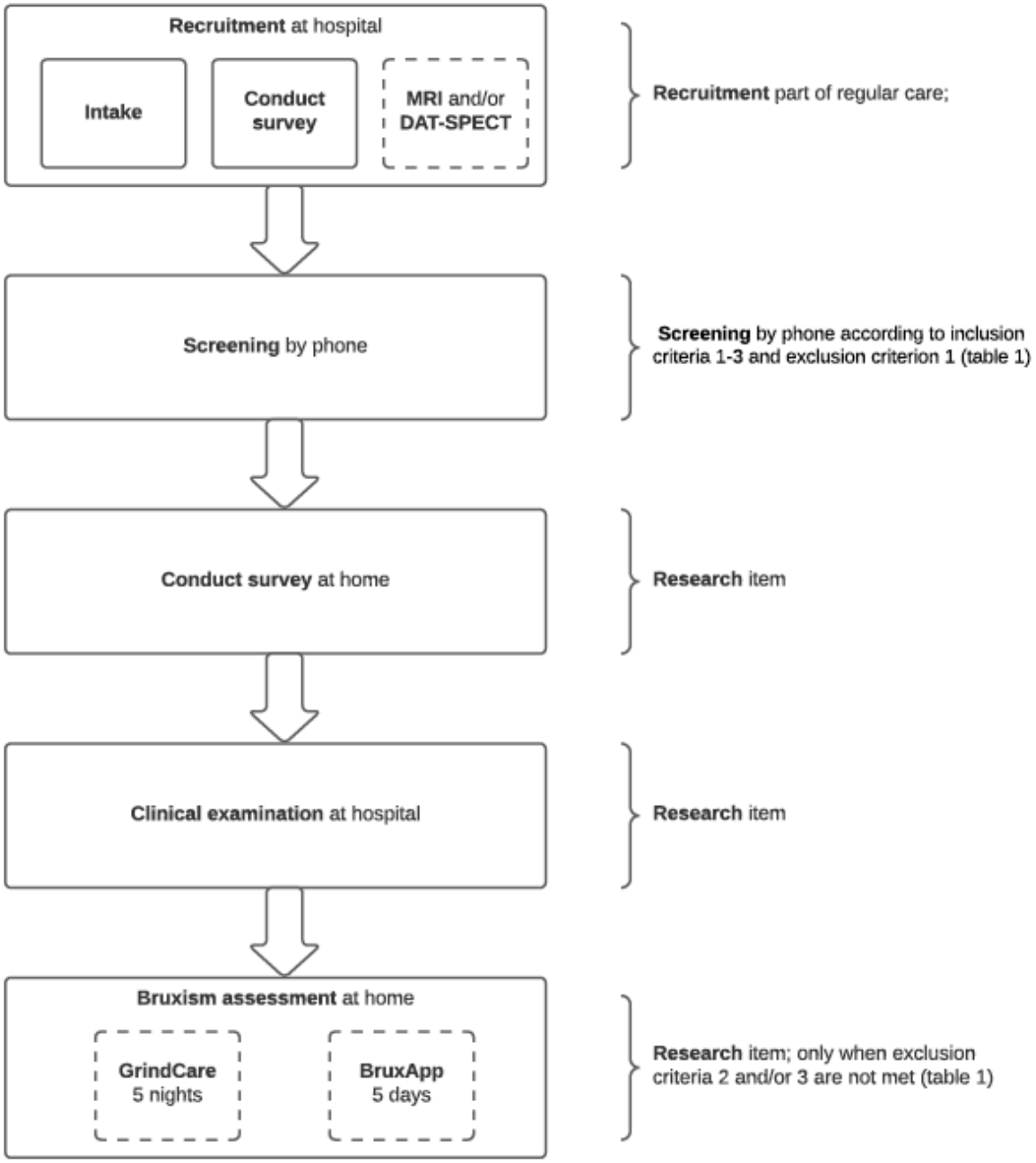

Figure 2. Flowchart of the study *in which a distinction was made between the attendance of participants at the hospital and the study components at the participant's home. The intake and first survey is part of the regular care at the hospital, and only followed by an additional MRI and/or DAT-SPECT 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).*

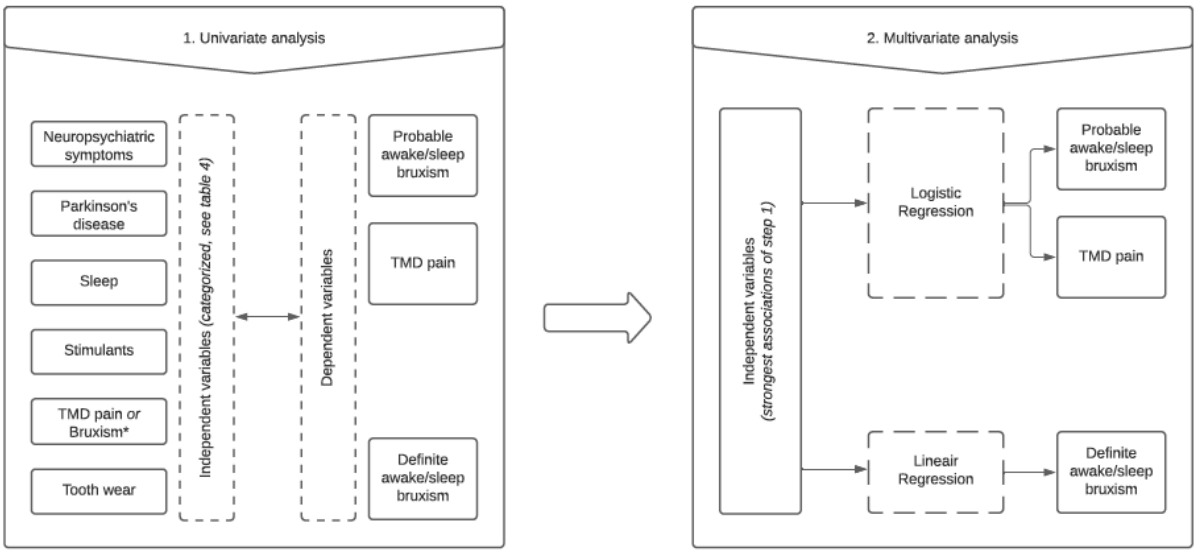

Figure 3. Flowchart of the data-analysis *related to the first secondary aim: "to investigate which factors are influencing the presence of probable awake/sleep bruxism, TMD pain and the frequency of definite awake/sleep bruxism". All variables will be tested individually to see whether an association 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.*

Appendix 1

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[46].
- *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"[48,64].
- *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)[44]. 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[65].

Non-motor symptoms:

- *Anxiety:* will be registered through the Parkinson Anxiety Scale (PAS)[51]. 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)[50]. 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)[44,66] and the Parkinson's Disease Cognitive Functional Rating Scale**, (**PD-CFRS)[42,67]. 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)[69,69]. 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)[53]. 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)[70]. 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[57] questionnaire that screens for the risk for moderate to severe obstructive sleep apnea (OSA), and the Scales for Outcomes PD Sleep (SCOPA-sleep)[54] 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)”[57]. 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)[55]. 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[62]. 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)[56]. 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)[58] 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)"[71]. 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)[72], 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)[73]. 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

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[25]. 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[73]. Consequently, 15 events are chosen and thus (4x15=) 60 events are needed. Based on the prevalence of the recent questionnaire-based pilot study[25], 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[25]. For the linear regression, this estimate of the sample size is sufficient to detect medium and large effect sizes[75]. 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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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
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Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	7

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	7-8
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7-8
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	n/a
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4,5,9-15
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,5 (+fig)
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4-5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	n/a

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4-5
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n/a
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	5
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	5
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	4-5
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	4-5
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	4-5,7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	7,8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a (dutch)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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Parkinson's disease, temporomandibular disorder pain, and bruxism and its clinical consequences. A protocol of a clinical observational study

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Parkinson's disease, temporomandibular disorder pain, and bruxism and its clinical consequences. A protocol of a clinical observational 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 clinical 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.

Trial registration: NL8307
Keywords: Parkinson's Disease; Temporomandibular Disorders; Bruxism; Tooth wear; Saliva; Protocol

Strengths and limitations of this study:

- This clinical study will provide accurate data on the presence of painful temporomandibular disorders and bruxism in Parkinson patients attending the outpatient clinic for movement disorders of Amsterdam UMC, location VUmc, and their possible associated factors like disease severity and medication usage.

- Novel information about tooth wear and saliva composition and quantity in patients with Parkinson's disease will be collected.
- Since polysomnographic recordings for the assessment of definite sleep bruxism are not feasible in this study, a portable, single-channel electromyographic recorder is used instead.
- Electromyographic recordings will be performed for several nights in a row, thus taking into account the fluctuating nature of sleep bruxism.
- Because of the design of this study, no causal relationships can be established between the outcome variables and predictors.

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 pain, anxiety, depression, sleep problems, and cognitive dysfunction[3,4].

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[5]. 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"[6]. It can occur during sleep, indicated as sleep bruxism, or during wakefulness, indicated as awake bruxism[6]. 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[7]. 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[7]. Both tooth wear and TMD may affect the oral health-related quality of life[8].

In a population with PD patients, oral health was recently studied[9]. 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[10]. Also, gastrointestinal problems are more frequently shown in patients with PD. In turn, this could influence the presence of tooth wear due to reflux[11,12].

While oral health care in PD has not been studied widely[9], 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 a condition that is considered to be regulated centrally and not peripherally[13]. In addition, in the pathophysiology of both PD and bruxism, the brain dopamine system plays an important role [14–16]. Besides, sleep disturbances[17] that are present both in PD[18] and in sleep bruxism, are associated with arousal activity[17,18]. As a result of such arousal activity, sleep bruxism may occur more frequently in people with sleep disturbances than in those without[19]. 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[20]. This is a characteristic that is also seen in sleep bruxism patients[21]. Furthermore, bruxism may be considered as a risk factor for TMD, depending on the assessment methods used[22]. 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[3,23]. Finally, suggestions have been put forward that alterations in the dopaminergic system are also present in patients with pain in the orofacial region[24], 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[25]. Also, PD patients reported a higher mean TMD-pain intensity than controls [25]. However, since this was a questionnaire-based study, extrapolation of these findings requires further verification through clinical and instrumental data. Hence, to overcome some of the limitations of the previous pilot study, 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[25], 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[26,27].

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[14], disease severity[13,15], psychosocial factors[28–30], and lifestyle factors[28,29,31] 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[12].
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 clinical 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.

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 ≥ 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 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)[32]. For the assessment of awake bruxism, patients will use, for 5 complete registration days, the BruxApp[33], which is a mobile application for the recording of bruxism activity based on ecological momentary assessment[6]. According to international consensus, a classification of the probability that bruxism is present can be made as follows: possible, probable, and definite bruxism presence[6]. 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)[6].

The TMD-pain diagnosis will be established according to the Diagnostic Criteria for TMD (DC/TMD)[34], 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[34].

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). Most of these variables have already been reported as possible risk factors for bruxism[29] and/or TMD[35] in the general population[28–30]. 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[36].

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[21]. Taking the cautious approach, we calculated the sample size for all conditions and chose the largest sample size. Aiming for a precision of 5% with a level of confidence of 95%, 382 participants are needed[37]. 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[36,38].

Patient and public involvement

Neither patients nor the community were involved in the design or performance of this study. However, feedback from participants of the earlier pilot study[21] was used to design this 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[21,39]. When quantifying bruxism with continuous data, recent insights showed a better quality of a definite bruxism diagnosis[6]. 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 a 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[6]. In addition, the clinical examination according to the DC/TMD[34] enables setting a valid TMD-pain diagnosis, making a distinction between several TMD complaints, and comparing the outcomes with other (inter-) national research.

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[40,41], 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[6]. 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[32]. 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[42]. This is an important issue, because such movement disorders can be present in patients with PD related to their medication usage. Fortunately, in the questionnaire and clinical examination of the MDS-UPDRS[43] (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.

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.

Ethics and dissemination:

This study protocol has been approved by the Medical Ethics Review Committee of Amsterdam UMC, location VUmc; NL. 2019.143). Informed consent will be obtained from all participants. A data monitor will meet annually to primarily concentrate on the safety of patients, and will be monitoring the collected data and informed consents.

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.

Authors contribution

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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Tandheelkunde (NWVT)), and the Dutch association for Orofacial Pain, Dysfunction and Prosthetic Dentistry (Nederlandse Vereniging voor Gnathologie en Prothethische Tandheelkunde (NVGPT)).

Competing interest

Dr. Lobbezoo reports grants and other from Sunstar Suisse SA, grants from Somnomed-Goedegebuure, grants from Airway Management, grants from Vivisol, grants from Health Holland, outside the submitted work.

Tables

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)[44]	**2**. for using the GrindCare: pacemaker
3. fulfil clinical diagnostic criteria for PD[45]	**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)[44];(Parkinson's Disease Cognitive Functional Rating Scale, PD-CFRS)[46]**
2.	**Disease stage (Hoehn & Yahr)[47]; Disease severity (Unified Parkinson's Disease Rating Scale – III, UPDRS-III)[43]**
3.	**Dopaminergic medication (Levodopa equivalent daily dose, LEDD)[48]**
4.	**Neuropsychiatric symptoms: Depression (Beck Depression Inventory-ii, BDI-ii)[49]; Apathy (Apathy evaluation scale, AES)[50]; Anxiety (Parkinson Anxiety Scale, PAS)[51]; Psychotic (Parkinson's Disease-adapted scale for assessment of positive symptoms, SAPS-PD)[52]; Impulse control (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, QUIP-RS)[53]**
5.	**Presynaptic dopaminergic loss, when applicable (brain imaging) (Dopamine Transporter Single Photon Emmission Computed Tomography, DAT-SPECT)[36,38]**
6.	**Quality of sleep (Scales for Outcomes PD Sleep, SCOPA-SLEEP)[54]**
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)[55]
	2. TMD pain (according to the Diagnostic Criteria for TMD, DC/TMD)[34] and intensity (graded chronic pain scale, GCPS)[56]
	3. Tooth wear
	4. Sleep (Obstructive Sleep Apnea, STOP-Bang NL)[57]
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))[34]
	2. Quantitative tooth wear screening (part of the Tooth Wear Evaluation System, TWES)[58]
	3. A brief screening of the dental prosthesis (when applicable)
	4. Dry mouth screening (Clinical Oral Dryness Score, CODS)[59]

	5. Jaw-mobility examination (DC/TMD)[34]
	6. Joint noises examination (DC/TMD)[34]
	7. Palpation of masticatory muscles and temporomandibular joints (DC/TMD)[34]
	8. Dynamic/static tests [60]
	9. Bruxoprovocationtest [61]
	10. Saliva test (Saliva-Check Buffer®)[62]
Registration	1. BruxApp [61]
	2. GrindCare® GC4[32,63]

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)

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Figure Legends

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 both conditions; 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.*

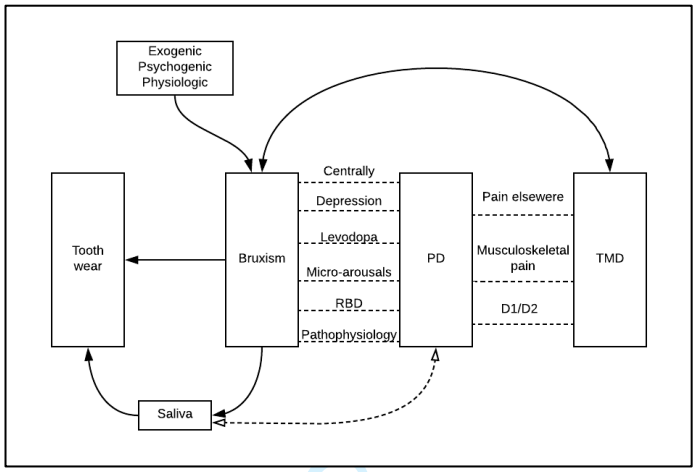

Figure 1. Visualization of the possible interactions between the different research variables. *Parkinson's Disease (PD) is associated with bruxism through different variables: the dopaminergic system (pathophysiology) plays a role in both conditions; the prodromal phase of PD (RBD) shows the same characteristics 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.*

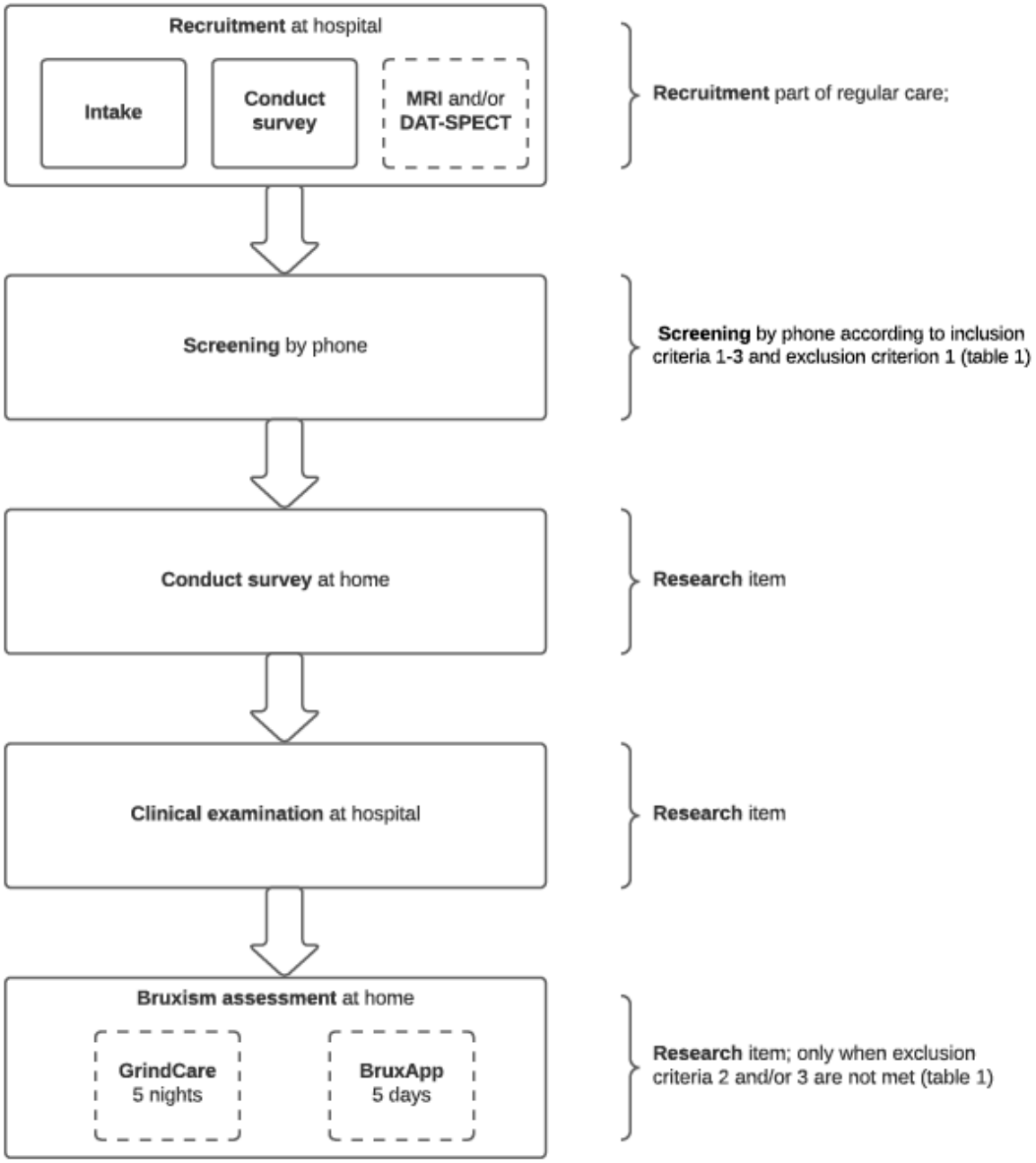

Figure 2. Flowchart of the study *in which a distinction was made between the attendance of participants at the hospital and the study components at the participant's home. The intake and first survey is part of the regular care at the hospital, and only followed by an additional MRI and/or DAT-SPECT 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).*

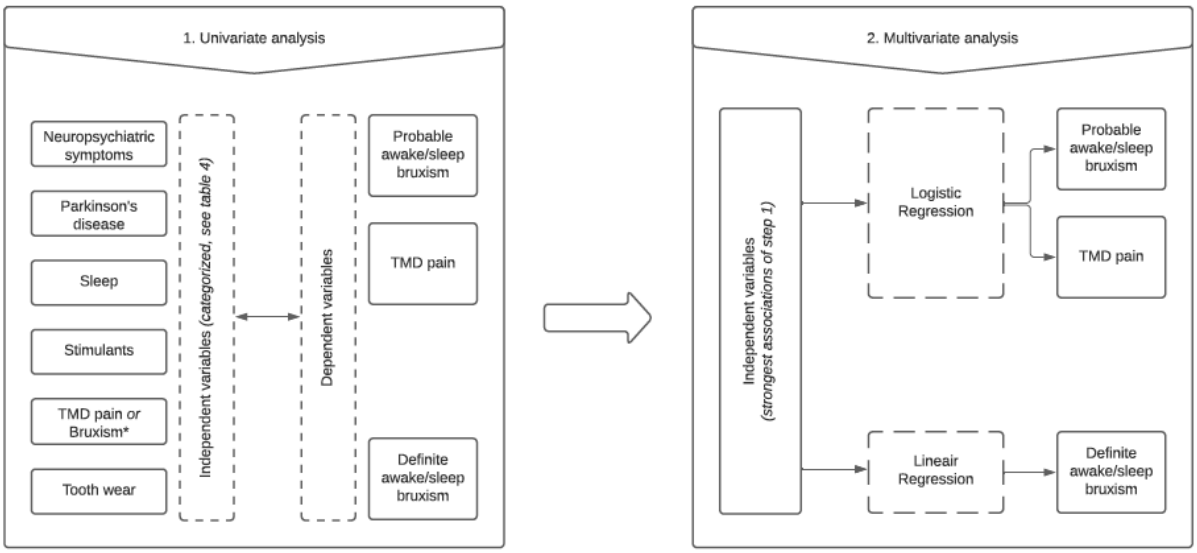

Figure 3. Flowchart of the data-analysis *related to the first secondary aim: "to investigate which factors are influencing the presence of probable awake/sleep bruxism, TMD pain and the frequency of definite awake/sleep bruxism". All variables will be tested individually to see whether an association 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.*

Appendix 1

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[47].
- *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"[48,64].
- *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)[43]. 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[65].

Non-motor symptoms:

- *Anxiety:* will be registered through the Parkinson Anxiety Scale (PAS)[51]. 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)[50]. 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)[44,66] and the Parkinson's Disease Cognitive Functional Rating Scale**, (**PD-CFRS)[46,67]. 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)[49,68,69]. 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)[53]. 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)[70]. 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[57] questionnaire that screens for the risk for moderate to severe obstructive sleep apnea (OSA), and the Scales for Outcomes PD Sleep (SCOPA-sleep)[54] 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)”[57]. 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)[55]. 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[62]. 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)[56]. 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)[58] 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)"[71]. 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)[72], 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)[73]. 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

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[25]. 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[74]. Consequently, 15 events are chosen and thus (4x15=) 60 events are needed. Based on the prevalence of the recent questionnaire-based pilot study[25], 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[25]. For the linear regression, this estimate of the sample size is sufficient to detect medium and large effect sizes[75]. 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

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	7
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	7

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	7-8
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7-8
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	n/a
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4,5,9-15
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,5 (+fig)
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4-5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	n/a

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4-5
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n/a
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	5
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	5
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	4-5
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	4-5
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	4-5,7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	7,8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a (dutch)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

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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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.

Trial registration: NL8307

Keywords: Parkinson's Disease; Temporomandibular Disorders; Bruxism; Tooth wear; Saliva; Protocol

Strengths and limitations of this study:

- This observational study will provide accurate data on the presence of painful temporomandibular disorders and bruxism in Parkinson patients attending the outpatient clinic for movement disorders of Amsterdam UMC, location VUmc, and their possible associated factors like disease severity and medication usage.
- Novel information about tooth wear and saliva composition and quantity in patients with Parkinson's disease will be collected.
- Since polysomnographic recordings for the assessment of definite sleep bruxism are not feasible in this study, a portable, single-channel electromyographic recorder is used instead.
- Electromyographic recordings will be performed for several nights in a row, thus taking into account the fluctuating nature of sleep bruxism.
- Because of the design of this study, no causal relationships can be established between the outcome variables and predictors.

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 a condition that 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.

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

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 ≥ 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%.

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®)[58 --56]
Registration	1. BruxApp [56 --57]
	2. GrindCare® GC4[59,60 ---58,59]

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[8]. 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)[8].

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].

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[61] 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 all conditions and chose the largest sample size. Aiming for a precision of 5% with a level of confidence of 95%, 246 participants are needed[62]. 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].

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)

Patient and public involvement

Neither patients nor the community were involved in the design or performance of this study. However, feedback from participants of the earlier pilot study[23] was used to design this 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[23,63]. When quantifying bruxism with continuous data, recent insights showed a better quality of a definite bruxism diagnosis[8]. 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[8]. This enables the analysis of continuous outcomes, which has been suggested by several

authors[64,65]. 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 scontributes to the feasibility of this protocol[8]. 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.

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[66,67], 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[8]. 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[68]. This is an important issue, because such movement disorders can be present in patients with PD related to their medication usage. 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.

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.

Ethics and dissemination:

This study protocol has been approved by the Medical Ethics Review Committee of Amsterdam UMC, location VUmc; NL. 2019.143). Informed consent will be obtained from all participants. A data monitor will meet annually to primarily concentrate on the safety of patients, and will be monitoring the collected data and informed consents. The results will be published in peer-reviewed journals, if relevant presented at conferences, and published as part of a Ph.D. thesis.

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.

Authors contribution

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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Competing interest

Dr. Lobbezoo reports grants and other from Sunstar Suisse SA, grants from Somnomed, grants from Airway Management, grants from Vivisol-Resmed, grants from Health Holland, outside the submitted work.

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Figure Legends

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 both conditions; 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.

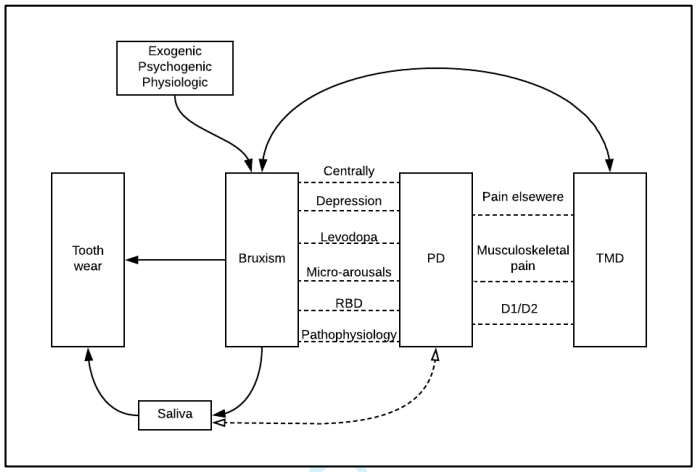

Figure 1. Visualization of the possible interactions between the different research variables. *Parkinson's Disease (PD) is associated with bruxism through different variables: the dopaminergic system (pathophysiology) plays a role in both conditions; the prodromal phase of PD (RBD) shows the same characteristics 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.*

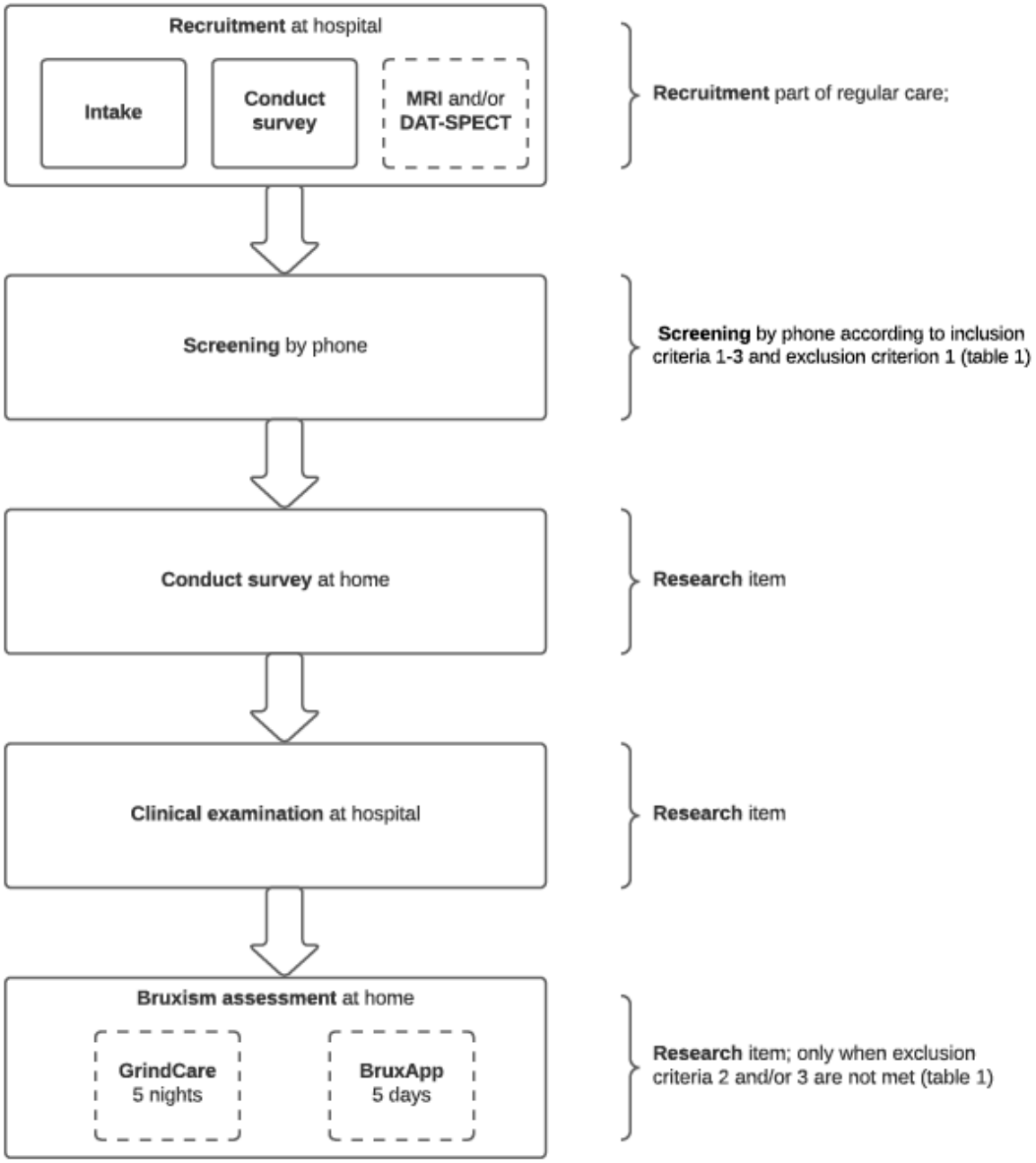

Figure 2. Flowchart of the study *in which a distinction was made between the attendance of participants at the hospital and the study components at the participant's home. The intake and first survey is part of the regular care at the hospital, and only followed by an additional MRI and/or DAT-SPECT 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).*

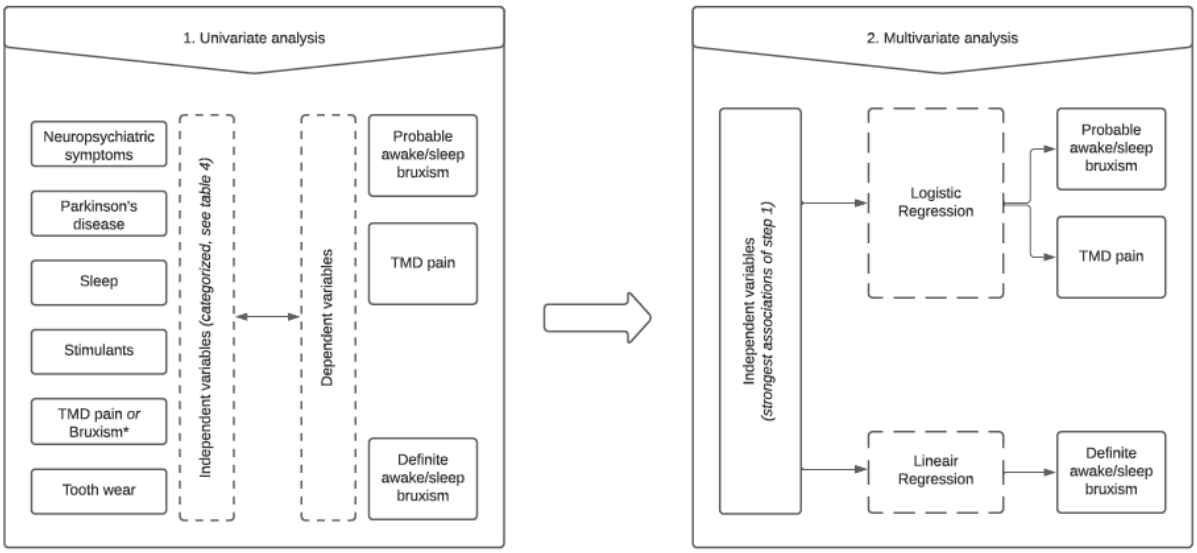

Figure 3. Flowchart of the data-analysis *related to the first secondary aim: "to investigate which factors are influencing the presence of probable awake/sleep bruxism, TMD pain and the frequency of definite awake/sleep bruxism". All variables will be tested individually to see whether an association 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.*

Appendix 1

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

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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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.

Trial registration: NL8307

Keywords: Parkinson's Disease; Temporomandibular Disorders; Bruxism; Tooth wear; Saliva; Protocol

Strengths and limitations of this study:

- This observational study will provide accurate data on the presence of painful temporomandibular disorders and bruxism in Parkinson patients attending the outpatient clinic for movement disorders of Amsterdam UMC, location VUmc, and their possible associated factors like disease severity and medication usage.
- Novel information about tooth wear and saliva composition and quantity in patients with Parkinson's disease will be collected.
- Since polysomnographic recordings for the assessment of definite sleep bruxism are not feasible in this study, a portable, single-channel electromyographic recorder is used instead.
- Electromyographic recordings will be performed for several nights in a row, thus taking into account the fluctuating nature of sleep bruxism.
- Because of the absence of a control group, no direct comparisons between individuals with PD and similar individuals without PD can be made.

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.

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

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 ≥ 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%.

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]

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].

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)

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.

Ethics and dissemination:

This study protocol has been approved by the Medical Ethics Review Committee of Amsterdam UMC, location VUmc; NL. 2019.143). Informed consent will be obtained from all participants. A data monitor will meet annually to primarily concentrate on the safety of patients, and will be monitoring the collected data and informed consents. The results will be published in peer-reviewed journals, if relevant presented at conferences, and published as part of a Ph.D. thesis.

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.

Authors contribution

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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Competing interest

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Figure Legends

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.*

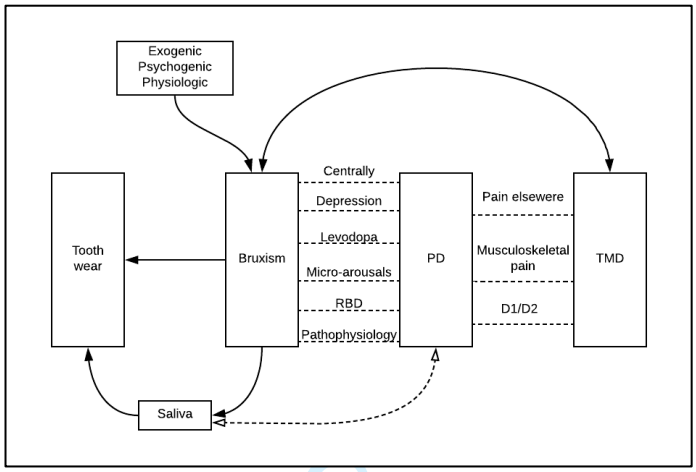

Figure 1. Visualization of the possible interactions between the different research variables. *Parkinson's Disease (PD) is associated with bruxism through different variables: the dopaminergic system (pathophysiology) plays a role in both conditions; the prodromal phase of PD (RBD) shows the same characteristics 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.*

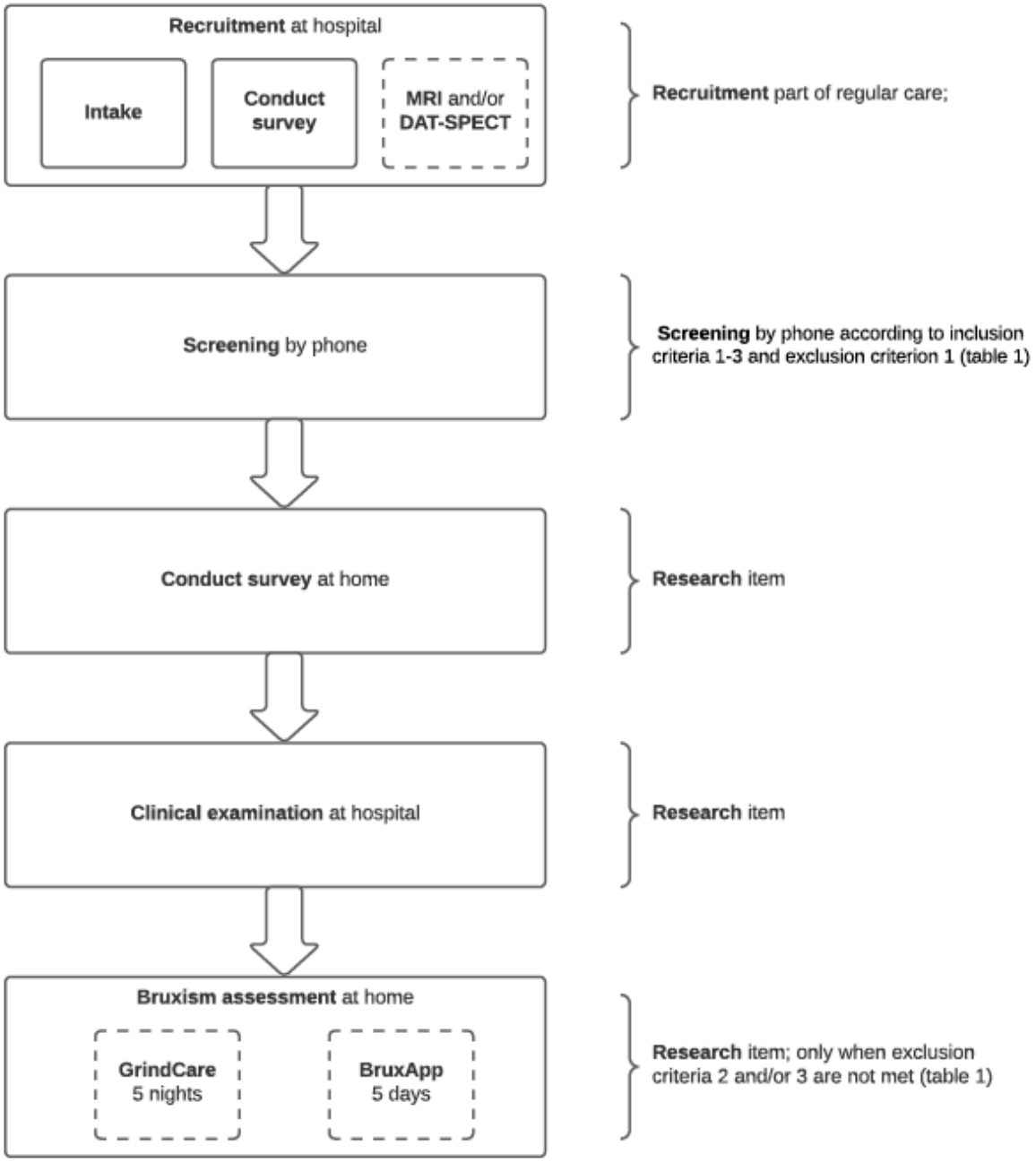

Figure 2. Flowchart of the study *in which a distinction was made between the attendance of participants at the hospital and the study components at the participant's home. The intake and first survey is part of the regular care at the hospital, and only followed by an additional MRI and/or DAT-SPECT 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).*

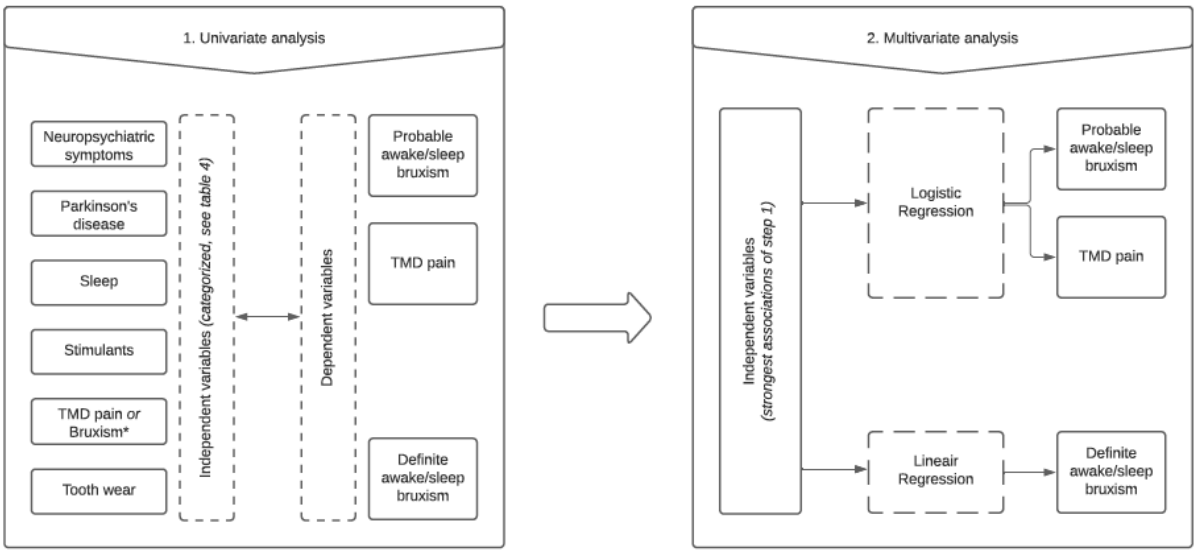

Figure 3. Flowchart of the data-analysis *related to the first secondary aim: "to investigate which factors are influencing the presence of probable awake/sleep bruxism, TMD pain and the frequency of definite awake/sleep bruxism". All variables will be tested individually to see whether an association 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.*

Appendix 1

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

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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