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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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Manuscripts

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 frequently⁵. 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 bruxism⁶. 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 structures⁷. 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 noises⁷. Both tooth wear and TMD may affect the oral health-related quality of life⁸.

In a population with PD patients, oral health was recently studied⁹. 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 environment¹⁰. 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 widely⁹, 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 peripherally¹³.

Also, in the pathophysiology of both PD and bruxism, the brain dopamine system plays an important role¹⁴⁻¹⁶. Besides, sleep disturbances¹⁷ that are present both in PD¹⁸ 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 without¹⁹. Also, in the prodromal phase of PD, a higher rhythmic masticatory muscle activity (RMMA) on polysomnography in NREM sleep has been observed, compared to controls²⁰. This is a characteristic that is also seen in sleep bruxism patients²¹. Furthermore, bruxism is considered as a risk factor for TMD²². TMD itself shares some characteristics with PD. For example, musculoskeletal pain (of which

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3 TMD pain is a subtype) is frequently reported by patients with PD^{3,23}. Finally, suggestions have been put
4 forward that alterations in the dopaminergic system are also present in patients with pain in the orofacial
5 region²⁴, although this remains to be confirmed in patients with TMD pain.
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9 Recently, a questionnaire-based pilot study in 368 patients with PD and 340 controls suggested a higher
10 prevalence of bruxism and TMD pain in patients with PD²⁵. Also, PD patients reported a higher mean TMD-pain
11 intensity than controls²⁵. However, since this was a questionnaire-based study, extrapolation of these findings
12 requires further verification through clinical data. To overcome some of the limitations of the previous pilot
13 study, the present protocol was designed. The planned study will acquire more objective clinical/instrumental
14 measures for awake and sleep bruxism and TMD pain, which can give more valid information on outcomes like
15 the prevalence of bruxism in this population. Also, additional factors, such as the severity of PD and cognitive
16 function, will be included as possible predictors for the presence of bruxism and/or TMD pain in PD patients.
17 Knowledge of the factors that can influence bruxism and/or TMD pain in patients with PD will help dentists
18 and other oral health care providers to provide individualised care to prevent and/or alleviate symptoms of
19 bruxism and/or TMD pain and their consequences in this vulnerable group of patients.
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27 Based on the above-summarized evidence, the primary aim of this study is to investigate the prevalence of
28 bruxism and TMD pain in PD patients, through objective measurements. Based on our pilot-study outcomes²⁵,
29 we hypothesise that the prevalence of bruxism and TMD pain in the current population will be higher than in
30 their peers without PD, described in the literature^{26,27}.
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35 In addition, the secondary aims and their corresponding hypotheses are the following:

- 36 1. To identify which factors are associated with the presence of bruxism and TMD pain in PD patients. We
37 hypothesise that factors like medication usage¹⁴, disease severity^{13,15}, psychosocial factors²⁸⁻³⁰, and
38 lifestyle factors^{28,29,31} are influencing the studied associations.
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- 40 2. To investigate whether the salivary flow, the pH, and the buffer capacity of saliva in patients with PD are
41 related to the severity of tooth wear. Our hypothesis is that in patients with PD, the saliva composition
42 and salivary flow deviate from normal standards and that this is associated with the severity of tooth
43 wear¹².
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- 45 3. To investigate with Dopamine Transporter Single Photon Emission Computed Tomography (DAT-SPECT)
46 whether there is a relationship between the degree of presynaptic dopaminergic loss and the presence of
47 bruxism in these patients. The hypothesis is that there is a difference in striatal dopaminergic deficit
48 between PD patients with and without bruxism, in which patients without bruxism show a smaller deficit.
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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 BruxApp³³, which is a mobile application for the recording of bruxism activity based on ecological momentary assessment⁶. According to international consensus, a classification of the probability that bruxism is present can be made as follows: possible, probable, and definite bruxism presence⁶. 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.

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3 The TMD-pain diagnosis will be established according to the Diagnostic Criteria for TMD (DC/TMD)³⁴, with the
4 use of standardized questionnaires and clinical examination procedures. Based on the collected data, the
5 following diagnoses can be set: myalgia (local myalgia, myofascial pain, myofascial pain with referral),
6 arthralgia, headache attributed to TMD, and non-painful joint disorders (disc displacement with reduction, disc
7 displacement with reduction with intermitted locking, disc displacement without reduction with limited mouth
8 opening, disc displacement without reduction without limited mouth opening, degenerative joint disease,
9 subluxation). The main focus of this research protocol will be the TMD-pain diagnosis, for the establishment of
10 which the diagnostic flow chart of the DC/TMD will be used³⁴.
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16 **Secondary study parameters**

17 To identify which factors are associated with the presence of bruxism and TMD pain in PD patients, several
18 variables will be evaluated (see Tables 2 and 3), using different clinical/instrumental measures (see appendix
19 1). Most of these variables have already been reported as risk factors for bruxism²⁹ and/or TMD³⁵ in the
20 general population²⁸⁻³⁰. However, the variables dopaminergic medication usage and disease stage/severity of
21 PD have not been studied yet in the association with bruxism or TMD pain. Finally, if DAT-SPECT imaging is
22 available, we will compare the measured presynaptic striatal dopaminergic deficit between participants with
23 and without bruxism³⁶.
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30 **Sample size**

31 According the pilot study, the prevalence of awake bruxism, sleep bruxism, and TMD pain in patients with PD is
32 46%, 24%, and 29.5%, respectively²¹. Taking the cautious approach, we calculated the sample size for all
33 conditions and chose the largest sample size. Aiming for a precision of 5% with a level of confidence of 95%,
34 382 participants are needed³⁷. See appendix 2 for the sample size calculation. Furthermore, the approach to
35 calculate the sample size for the most important secondary aim (viz., to identify which factors are associated
36 with the presence of bruxism and TMD pain in PD patients) is also shown in appendix 2. The numbers are
37 obtained when reaching the sample size for the primary aim.
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44 **Statistical approach**

45 With the use of descriptive tests, demographic data will be summarised. In Figure 3, it is shown how the
46 dataset is analysed to give an answer on which factor is associated with the presence/absence of probable
47 bruxism/TMD pain or with the frequency of definite bruxism. The forward selection procedure will be used for
48 the (strongest) independent variables (see Table 4) until all variables in this regression model show a P-value
49 <0.05 (See Step 2, Figure 3). Finally, to analyse if there is an association between tooth wear and composition
50 of saliva, Spearman's correlation coefficient will be used. For the DAT-SPECT, a semi-quantitative analysis will
51 be used. Ratios for specific versus non-specific binding will be calculated for the regions of interest and
52 analysed using the independent sample t-test^{36,38}.
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59 **Patient and public involvement**

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3 Neither patients nor the community were involved in the design or performance of this study. However,
4 feedback from participants of the earlier pilot study²¹ was used to design this study. The burden for the
5 participants will be kept as minimal as possible. On request, the outcomes of this study will be disseminated to
6 the participants.
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10 Discussion

11 The primary aim of this study is to objectively measure the prevalence of bruxism and TMD pain in a
12 population of patients with Parkinson's Disease (PD). Furthermore, the three secondary aims are described as
13 follows: (i) to identify which factors are associated with the presence of bruxism and TMD pain in PD patients,
14 (ii) to investigate whether the salivary flow, the pH, and the buffer capacity of saliva in patients with PD are
15 related to the severity of tooth wear, and finally (iii) to investigate with DAT-SPECT whether there is a
16 relationship between the degree of presynaptic dopaminergic loss and the presence of bruxism in these
17 patients.
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24 To the best of our knowledge, this is the first study that attempts to objectively measure the prevalence of
25 awake bruxism, sleep bruxism, and TMD pain in a population of patients with PD. Previous studies investigated
26 the prevalence of awake bruxism in this population, however only few participants were included or only
27 questionnaires were used^{21,39}. Furthermore, in the present study, the use of the GrindCare® GC4 and the
28 BruxApp can give more certainty towards a definite establishment of sleep and awake bruxism, respectively⁶.
29 In addition, the clinical examination according to the DC/TMD³⁴ enables setting a valid TMD-pain diagnosis,
30 making a distinction between several TMD complaints, and comparing the outcomes with other (inter-
31 national research.
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38 Because PD patients are vulnerable and burdened with frequent visits to multiple caregivers (e.g., their
39 neurologist, physiotherapist, and speech therapist), it is important to burden the participants as minimally as
40 possible. Therefore, during the process of designing this study and collecting the data, a multidisciplinary
41 approach was established between neurologists and dentists to enable an as efficient as possible usage of the
42 patient's time and energy.
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47 The targeted number of inclusions will be a challenge. However, the calculated sample size is an estimation,
48 because no clinical prevalences are known as yet. Like in otherwise healthy individuals, clenching and grinding
49 are not always recognized by the patients themselves^{40,41}, thus the prevalence of sleep bruxism in the pilot
50 study could have been underestimated. This means that the calculated sample size in this study might be
51 higher than eventually required. Therefore, an interim analysis will be performed after 130 included
52 participants or 6 months.
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57 This study has no longitudinal character and therefore, no causal relations can be observed between the (in-
58 dependent variables. Also, polysomnography is the golden standard to detect sleep bruxism while in the
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3 present study, a portable electromyographic recorder will be used⁶. However, since this device will be used for
4 several nights in a row, the fluctuating character of sleep bruxism can be taken into account and is therefore
5 considered a good proxy for definite sleep bruxism³². It should be noted, however, that the portable recorder
6 will fail to enable a distinction between jaw-muscle activities related to sleep bruxism and those related to
7 other orofacial movement disorders like oral dyskinesia and oro-mandibular dystonia⁴³. This is an important
8 issue, because such movement disorders can be present in patients with PD related to their medication usage.
9 Fortunately, in the questionnaire and clinical examination of the MDS-UPDRS⁴⁴ (Table 2), the presence of oral
10 dyskinesia and oro-mandibular dystonia is included. Hence, it is possible to correct for their presence in the
11 data analysis.
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18 In conclusion, this study will give more detailed information about the prevalence of bruxism and TMD pain in
19 patients with PD, as well as about possible associated factors like medication usage and severity of the disease.
20 Finally, more clinically relevant information will become available for dentists and other oral health care
21 professionals about the amount of tooth wear and the composition of saliva in patients with PD.
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25 **Ethics and dissemination:**

26 This study protocol has been approved by the Medical Ethics Review Committee of Amsterdam UMC, location
27 VUmc; NL. 2019.143). Informed consent will be obtained from all participants. A data monitor will meet
28 annually to primarily concentrate on the safety of patients, and will be monitoring the collected data and
29 informed consents.
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34 Due to the sensitive nature of personal information, all data will be blinded and stored in secure
35 environments. Only the executive researcher and the head of the department can reach the unblinded
36 informed consents and the key for unblinding. These are stored separately. Digital data will be stored
37 pseudonymized in a secure database using Castor EDC (CDISC, Amsterdam, Netherlands). Detailed methods for
38 data management and storage can be obtained by contacting the corresponding author.
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43 **Authors contribution**

44 All authors were involved in designing this study. MV obtained the approval of the Medical Ethics Review
45 Committee and drafted the manuscript. Finally, all authors gave feedback on the draft and approved the final
46 manuscript.
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50 **Funding statement:**

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52 & Parkinson), the Dutch association for scientific dentistry (Nederlandse Wetenschappelijke Vereniging voor
53 Tandheelkunde (NWVT)), and the Dutch association for Orofacial Pain, Dysfunction and Prosthetic Dentistry
54 (Nederlandse Vereniging voor Gnathologie en Prothetische Tandheelkunde (NVGPT)).
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Competing interest

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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 Emission 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. Bruxoprovoctiontest 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.

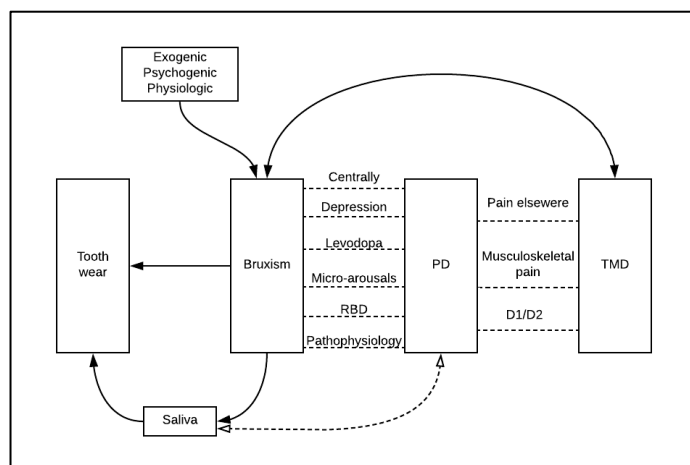


Figure 1. Visualization of the possible interactions between the different research variables. *Parkinson’s Disease (PD)* is associated with bruxism through different variables: the dopaminergic system (pathophysiology) plays a role in both conditions; the prodromal phase of PD (RBD) shows the same characteristics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

view only

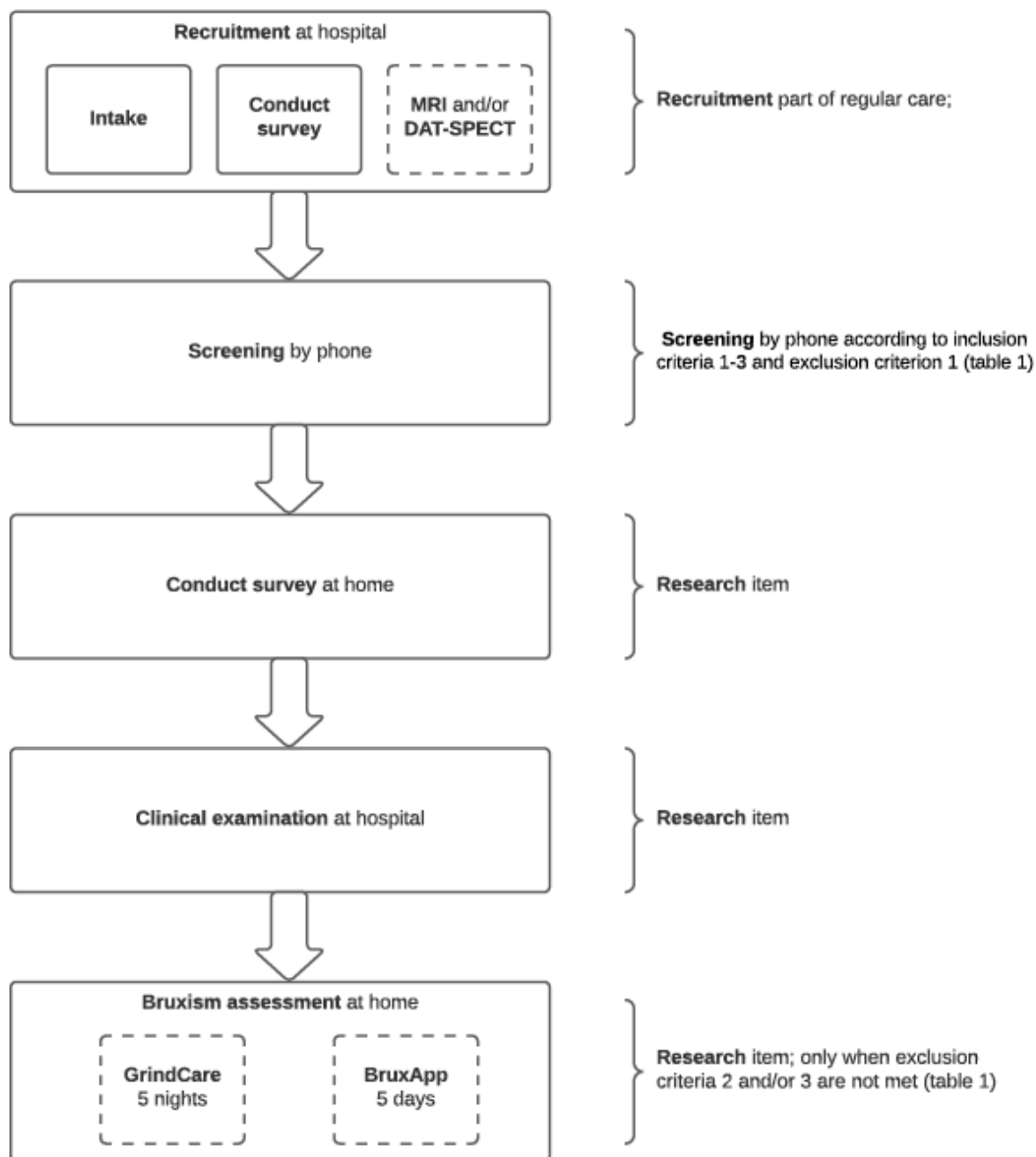


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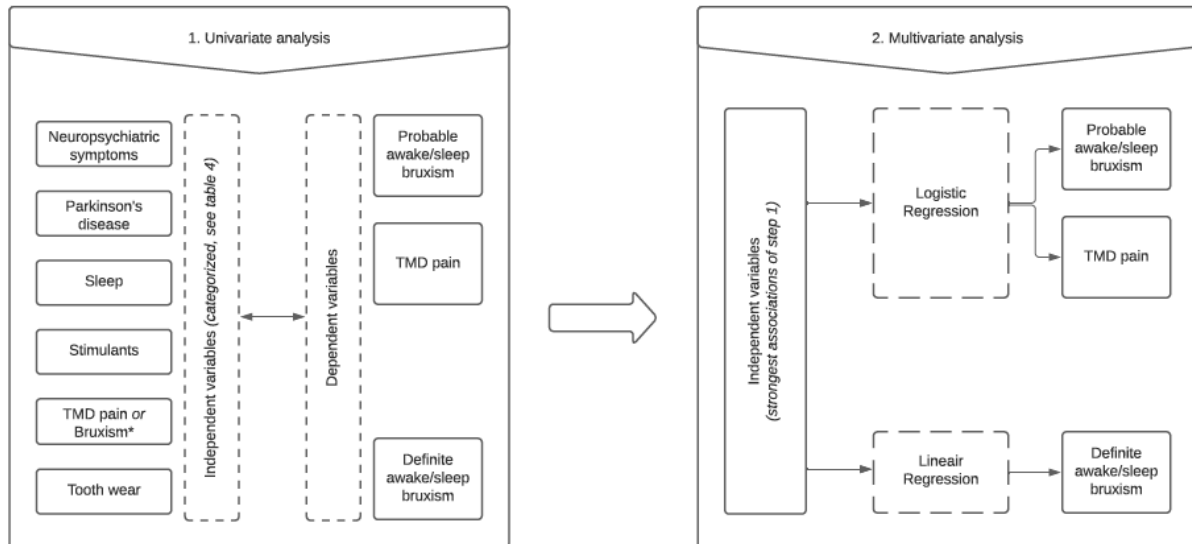


Figure 3. Flowchart of the data-analysis related to the first secondary aim: “to investigate which factors are influencing the presence of probable awake/sleep bruxism, TMD pain and the frequency of definite awake/sleep bruxism”. All variables will be tested individually to see whether an association 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 stage⁴⁶.
- 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 \leq 32)”, “moderate (score 33-58)”, and “severe (score \geq 59)” motor problems⁶⁵.

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 \geq 11 on that subscale)”, “episodic anxiety (score \geq 6 on that subscale)”, “avoidance behavior (score \geq 5 on that subscale)”, and “any anxiety disorder score (score \geq 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-NL⁵⁷ 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 screened⁶². 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 $\leq 1/3$ (score 2)", "loss of crown height $>1/3$ but $<2/3$ (score 3)" and "loss of crown height $\geq 2/3$ (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 reported²⁵. The prevalence found for these outcome measures were **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 needed⁷³. Consequently, 15 events are chosen and thus (4x15=) 60 events are needed. Based on the prevalence of the recent questionnaire-based pilot study²⁵, 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 needed²⁵. For the linear regression, this estimate of the sample size is sufficient to detect medium and large effect sizes⁷⁵. 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.

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

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.

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

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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
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

1	Roles and	#5b	Name and contact information for the trial sponsor	7-8
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	7-8
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
22				
23				
24	Introduction			
25				
26				
27	Background and	#6a	Description of research question and justification for undertaking	2-3
28	rationale		the trial, including summary of relevant studies (published and	
29			unpublished) examining benefits and harms for each intervention	
30				
31				
32	Background and	#6b	Explanation for choice of comparators	4
33	rationale: choice of			
34	comparators			
35				
36				
37	Objectives	#7	Specific objectives or hypotheses	3
38				
39				
40	Trial design	#8	Description of trial design including type of trial (eg, parallel	4
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
44				
45				
46	Methods:			
47	Participants,			
48	interventions, and			
49	outcomes			
50				
51				
52				
53	Study setting	#9	Description of study settings (eg, community clinic, academic	4
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
56				
57				
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1	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
2				
3				
4				
5				
6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	n/a
7	description			
8				
9				
10	Interventions:	#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
11	modifications			
12				
13				
14				
15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
16	adherence			
17				
18				
19				
20	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
21	concomitant care			
22				
23				
24	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
25				
26				
27				
28				
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30				
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32				
33				
34	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)
35				
36				
37				
38				
39				
40	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
41				
42				
43				
44				
45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4-5
46				
47				
48				
49	Methods: Assignment			
50	of interventions (for			
51	controlled trials)			
52				
53				
54	Allocation: sequence	#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
55	generation			
56				
57				
58				
59				
60				

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

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	5
2	analyses		analyses)	
3				
4	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	5
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
8				
9				
10	Methods: Monitoring			
11				
12	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of	5
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
18				
19				
20				
21				
22	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	5
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
26				
27	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	4-5
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
31				
32				
33	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	4-5
34			whether the process will be independent from investigators and	
35			the sponsor	
36				
37				
38	Ethics and			
39	dissemination			
40				
41				
42	Research ethics	#24	Plans for seeking research ethics committee / institutional review	7
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	7
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
50				
51				
52				
53	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial	4
54			participants or authorised surrogates, and how (see Item 32)	
55				
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1	Consent or assent:	#26b	Additional consent provisions for collection and use of	n/a
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
4				
5				
6	Confidentiality	#27	How personal information about potential and enrolled	4-5,7
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
9				
10				
11	Declaration of interests	#28	Financial and other competing interests for principal investigators	8
12			for the overall trial and each study site	
13				
14				
15	Data access	#29	Statement of who will have access to the final trial dataset, and	7
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
19				
20	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for	n/a
21	care		compensation to those who suffer harm from trial participation	
22				
23				
24	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results	7
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
29				
30				
31				
32				
33	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	7,8
34	authorship		professional writers	
35				
36				
37	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	7
38	reproducible research		participant-level dataset, and statistical code	
39				
40				
41	Appendices			
42				
43	Informed consent	#32	Model consent form and other related documentation given to	n/a
44	materials		participants and authorised surrogates	(dutch)
45				
46				
47	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
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BMJ Open

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

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Manuscripts

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.

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2
3 51 - Novel information about tooth wear and saliva composition and quantity in patients with Parkinson's
4 52 disease will be collected.
5 53 - Since polysomnographic recordings for the assessment of definite sleep bruxism are not feasible in this
6 54 study, a portable, single-channel electromyographic recorder is used instead.
7 55 - Electromyographic recordings will be performed for several nights in a row, thus taking into account the
8 56 fluctuating nature of sleep bruxism.
9 57 - Because of the design of this study, no causal relationships can be established between the outcome
10 58 variables and predictors.
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13 59

60 Introduction

61 Parkinson's disease (PD) is a neurodegenerative movement disorder characterized by motor symptoms, in
62 particular rigidity, bradykinesia, and tremor^{1,2}. Patients with PD do not solely experience motor symptoms, but
63 also non-motor symptoms like pain, anxiety, depression, sleep problems, and cognitive dysfunction^{3,4}.

64
65 Due to global ageing, the prevalence of PD is estimated to increase significantly in the near future. Ageing is
66 associated with oral health-related issues, which may therefore occur more frequently in the near future as
67 well⁵. Dentists regularly see patients with bruxism in the dental office, which is an oral health-related issue
68 that is not necessarily associated with systemic diseases. Bruxism is currently defined as "a repetitive jaw-
69 muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the
70 mandible"⁶. It can occur during sleep, indicated as sleep bruxism, or during wakefulness, indicated as awake
71 bruxism⁶. Not only bruxism itself, but also its possible consequences, such as mechanical tooth wear and
72 temporomandibular disorders (TMD), have hardly been studied in patients with PD. TMD is a collective term
73 embracing disorders of the temporomandibular joint, masticatory muscles, and adjacent anatomical
74 structures⁷. TMD can present as painful and non-painful conditions. Patients with TMD can report, for
75 example, orofacial pain (including headache), limitations in the movement of the mandible, and joint noises⁷.
76 Both tooth wear and TMD may affect the oral health-related quality of life⁸.

77
78 In a population with PD patients, oral health was recently studied⁹. It was shown that the oral health in PD
79 patients is deteriorated as compared to their peers without PD. Besides, medication usage can influence
80 salivation production, which in turn influences the oral environment¹⁰. Also, gastrointestinal problems are
81 more frequently shown in patients with PD. In turn, this could influence the presence of tooth wear due to
82 reflux^{11,12}.

83
84 While oral health care in PD has not been studied widely⁹, oral (dys-)function in PD has been studied even less,
85 even though PD, bruxism, and TMD have been suggested to share several common characteristics (see Figure
86 1). Similar to PD, bruxism is a condition that is considered to be regulated centrally and not peripherally¹³. In
87 addition, in the pathophysiology of both PD and bruxism, the brain dopamine system plays an important role
88 ¹⁴⁻¹⁶. Besides, sleep disturbances¹⁷ that are present both in PD¹⁸ and in sleep bruxism, are associated with
89 arousal activity^{17,18}. As a result of such arousal activity, sleep bruxism may occur more frequently in people
90 with sleep disturbances than in those without¹⁹. Also, in the prodromal phase of PD, a higher rhythmic

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2
3 91 masticatory muscle activity (RMMA) on polysomnography in NREM sleep has been observed, compared to
4 92 controls²⁰. This is a characteristic that is also seen in sleep bruxism patients²¹. Furthermore, bruxism may be
5 93 considered as a risk factor for TMD, depending on the assessment methods used²². TMD itself shares some
6 94 characteristics with PD. For example, musculoskeletal pain (of which TMD pain is a subtype) is frequently
7 95 reported by patients with PD^{3,23}. Finally, suggestions have been put forward that alterations in the
8 96 dopaminergic system are also present in patients with pain in the orofacial region²⁴, although this remains to
9 97 be confirmed in patients with TMD pain.
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15 99 Recently, a questionnaire-based pilot study in 368 patients with PD and 340 controls suggested a higher
16 100 prevalence of bruxism and TMD pain in patients with PD²⁵. Also, PD patients reported a higher mean TMD-pain
17 101 intensity than controls²⁵. However, since this was a questionnaire-based study, extrapolation of these findings
18 102 requires further verification through clinical and instrumental data. Hence, to overcome some of the
19 103 limitations of the previous pilot study, the present protocol was designed. The planned study will acquire more
20 104 objective clinical and instrumental measures for awake and sleep bruxism and TMD pain, which can give more
21 105 valid information on outcomes like the presence of bruxism in this population. Also, additional factors, such as
22 106 the severity of PD and cognitive function, will be included as possible predictors for bruxism and/or TMD pain
23 107 in PD patients. Knowledge of the factors that can influence bruxism and/or TMD pain in patients with PD will
24 108 help dentists and other oral health care providers to provide individualised care to prevent and/or alleviate
25 109 symptoms of bruxism and/or TMD pain and their consequences in this vulnerable group of patients.
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34 111 Based on the above-summarized evidence, the primary aim of this study is to investigate the presence of
35 112 bruxism and TMD pain in PD patients, through objective clinical and instrumental measurements. Based on our
36 113 pilot-study outcomes²⁵, we hypothesise that the prevalence of bruxism and TMD pain in the current
37 114 population will be higher than in their peers without PD, as described in the literature^{26,27}.
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41

42 116 In addition, the secondary aims and their corresponding hypotheses are the following:

- 43 117 1. To identify which factors are associated with bruxism and TMD pain in PD patients. We hypothesise that
44 118 factors like medication usage¹⁴, disease severity^{13,15}, psychosocial factors²⁸⁻³⁰, and lifestyle factors^{28,29,31}
45 119 are influencing the studied associations.
- 46 120 2. To investigate whether the salivary flow, the pH, and the buffer capacity of saliva in patients with PD are
47 121 related to the severity of tooth wear. Our hypothesis is that in patients with PD, the saliva composition
48 122 and salivary flow deviate from normal standards and that this is associated with the severity of tooth
49 123 wear¹².
- 50 124 3. To investigate with Dopamine Transporter Single Photon Emission Computed Tomography (DAT-SPECT)
51 125 whether there is a relationship between the degree of presynaptic dopaminergic loss and the presence of
52 126 bruxism in these patients. The hypothesis is that there is a difference in striatal dopaminergic deficit
53 127 between PD patients with and without bruxism, in which patients without bruxism show a smaller deficit.
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129 **Methods and analysis**

130 The design of this study is a single-centre observational clinical study that will take place at the Department of
131 Neurology of the Amsterdam University Medical Centres (Amsterdam UMC), location VUmc. The data
132 collection will take place for two years.

133

134 **Participants and eligibility**

135 Patients already clinically diagnosed with PD or planned for an intake appointment with presumable PD at the
136 outpatient clinic for movement disorders of the VUmc, will be eligible to participate in the study. Yearly, about
137 100-120 new consultations for PD are seen in the outpatient clinic. In addition, patients already receiving
138 treatment at the VUmc are eligible for participation as well. The inclusion and exclusion criteria are listed in
139 Table 1.

140

141 **Study procedure**

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

150

151 **Main study parameters**

152 The main study parameters or endpoints are “presence of bruxism (sleep and/or awake)” as well as “diagnosis
153 of TMD pain”. For the assessment of sleep bruxism, patients will be asked to sleep 5 complete registration
154 nights with a portable, single-channel electromyographic recorder, viz., the GrindCare® GC4 (Sunstar Suisse SA,
155 Etoy, Switzerland)³². For the assessment of awake bruxism, patients will use, for 5 complete registration days,
156 the BruxApp³³, which is a mobile application for the recording of bruxism activity based on ecological
157 momentary assessment⁶. According to international consensus, a classification of the probability that bruxism
158 is present can be made as follows: possible, probable, and definite bruxism presence⁶. In this research, all
159 probabilities of bruxism presence can be determined, however, the highest probability will be used (viz., both
160 probable and definite). When patients cannot use the GrindCare® GC4 and/or BruxApp, and more certainty
161 towards a definite presence is thus impossible, probable bruxism presence will be determined with the use of
162 data from the clinical examination, based on the presence of positive symptoms of bruxism (viz., clenching
163 marks in the soft tissues of the cheek, tongue, or lip, mechanical tooth wear (attrition), and/or hypertrophy of
164 the masseter muscle)⁶.

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2
3 165 The TMD-pain diagnosis will be established according to the Diagnostic Criteria for TMD (DC/TMD)³⁴, with the
4 166 use of standardized questionnaires and clinical examination procedures. Based on the collected data, the
5 167 following diagnoses can be set: myalgia (local myalgia, myofascial pain, myofascial pain with referral),
6 168 arthralgia, headache attributed to TMD, and non-painful joint disorders (disc displacement with reduction, disc
7 169 displacement with reduction with intermitted locking, disc displacement without reduction with limited mouth
8 170 opening, disc displacement without reduction without limited mouth opening, degenerative joint disease,
9 171 subluxation). The main focus of this research protocol will be the TMD-pain diagnosis, for the establishment of
10 172 which the diagnostic flow chart of the DC/TMD will be used³⁴.

16 173 **Secondary study parameters**

17 174 To identify which factors are associated with bruxism and TMD pain in PD patients, several variables will be
18 175 evaluated (see Tables 2 and 3), using different clinical/instrumental measures (see appendix 1). Most of these
19 176 variables have already been reported as possible risk factors for bruxism²⁹ and/or TMD³⁵ in the general
20 177 population²⁸⁻³⁰. However, the variables dopaminergic medication usage and disease stage/severity of PD have
21 178 not been studied yet in the association with bruxism or TMD pain in PD patients. Finally, if DAT-SPECT imaging
22 179 is available, we will compare the measured presynaptic striatal dopaminergic deficit between participants with
23 180 and without bruxism³⁶.

28 181 29 182 **Sample size**

30 183 According the pilot study, the prevalence of awake bruxism, sleep bruxism, and TMD pain in patients with PD is
31 184 46%, 24%, and 29.5%, respectively²¹. Taking the cautious approach, we calculated the sample size for all
32 185 conditions and chose the largest sample size. Aiming for a precision of 5% with a level of confidence of 95%,
33 186 382 participants are needed³⁷. See appendix 2 for the sample size calculation. Furthermore, the approach to
34 187 calculate the sample size for the most important secondary aim (viz., to identify which factors are associated
35 188 with bruxism and TMD pain in PD patients) is also shown in appendix 2. The numbers are obtained when
36 189 reaching the sample size for the primary aim.

42 190 43 191 **Statistical approach**

44 192 With the use of descriptive tests, demographic data will be summarised. In Figure 3, it is shown how the
45 193 dataset is analysed to give an answer on which factor is associated with the presence/absence of probable
46 194 bruxism/TMD pain or with the frequency (i.e., the number of bruxism events per hour) of definite bruxism. The
47 195 forward selection procedure will be used for the (strongest) independent variables (see Table 4) until all
48 196 variables in this regression model show a P-value <0.05 (See Step 2, Figure 3). Finally, to analyse if there is an
49 197 association between tooth wear and composition of saliva, Spearman's correlation coefficient will be used. For
50 198 the DAT-SPECT, a semi-quantitative analysis will be used. Ratios for specific versus non-specific binding will be
51 199 calculated for the regions of interest (viz., left and right putamen and caudate nucleus, using the occipital
52 200 cortex as a reference area) and analysed using the independent sample t-test^{36,38}.

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202 Patient and public involvement

203 Neither patients nor the community were involved in the design or performance of this study. However,
204 feedback from participants of the earlier pilot study²¹ was used to design this study. The burden for the
205 participants will be kept as minimal as possible. On request, the outcomes of this study will be disseminated to
206 the participants.

207 Discussion

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

214
215 To the best of our knowledge, this is the first study that attempts to objectively measure the presence of
216 awake bruxism, sleep bruxism, and TMD pain in a population of patients with PD. Previous studies investigated
217 the prevalence of awake bruxism in this population, however only few participants were included or only
218 questionnaires were used^{21,39}. When quantifying bruxism with continuous data, recent insights showed a
219 better quality of a definite bruxism diagnosis⁶. Nevertheless, we used a dichotomous outcome in this protocol
220 study to answer our first aim, i.e., to investigate the presence of bruxism. Besides, we also included self-report
221 and a clinical data, which do not yield continuous outcomes. Despite this, in the present study, the use of the
222 GrindCare[®] GC4 and the BruxApp can give more certainty towards a definite establishment of sleep and awake
223 bruxism, respectively⁶. In addition, the clinical examination according to the DC/TMD³⁴ enables setting a valid
224 TMD-pain diagnosis, making a distinction between several TMD complaints, and comparing the outcomes with
225 other (inter-) national research.

226
227 Because PD patients are vulnerable and burdened with frequent visits to multiple caregivers (e.g., their
228 neurologist, physiotherapist, and speech therapist), it is important to burden the participants as minimally as
229 possible. Therefore, during the process of designing this study and collecting the data, a multidisciplinary
230 approach was established between neurologists and dentists to enable an as efficient as possible usage of the
231 patient's time and energy.

232
233 The targeted number of inclusions will be a challenge. However, the calculated sample size is an estimation,
234 because no clinical prevalences are known as yet. Like in otherwise healthy individuals, clenching and grinding
235 are not always recognized by the patients themselves^{40,41}, thus the prevalence of sleep bruxism in the pilot
236 study could have been underestimated. This means that the calculated sample size in this study might be
237 higher than eventually required. Therefore, an interim analysis will be performed after 130 included
238 participants or 6 months.

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5 240 This study has no longitudinal character and therefore, no causal relations can be observed between the (in-
6 241 dependent variables. Also, polysomnography is the golden standard to detect sleep bruxism while in the
7
8 242 present study, a portable electromyographic recorder will be used⁶. However, since this device will be used for
9
10 243 several nights in a row, the fluctuating character of sleep bruxism can be taken into account and is therefore
11 244 considered a good proxy for definite sleep bruxism³². It should be noted, however, that the portable recorder
12 245 will fail to enable a distinction between jaw-muscle activities related to sleep bruxism and those related to
13
14 246 other orofacial movement disorders like oral dyskinesia and oro-mandibular dystonia⁴². This is an important
15 247 issue, because such movement disorders can be present in patients with PD related to their medication usage.
16
17 248 Fortunately, in the questionnaire and clinical examination of the MDS-UPDRS⁴³ (Table 2), the presence of oral
18 249 dyskinesia and oro-mandibular dystonia is included. Hence, it is possible to correct for their presence in the
19
20 250 data analysis.

21 251
22
23 252 In conclusion, this study will give more detailed information about the presence of bruxism and TMD pain in
24 253 patients with PD, as well as about possible associated factors like medication usage and severity of the disease.
25
26 254 Finally, more clinically relevant information will become available for dentists and other oral health care
27
28 255 professionals about the amount of tooth wear and the composition of saliva in patients with PD.

29 30 256 **Ethics and dissemination:**

31
32 257 This study protocol has been approved by the Medical Ethics Review Committee of Amsterdam UMC, location
33 258 VUmc; NL. 2019.143). Informed consent will be obtained from all participants. A data monitor will meet
34
35 259 annually to primarily concentrate on the safety of patients, and will be monitoring the collected data and
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37 260 informed consents.

38 261
39 262 Due to the sensitive nature of personal information, all data will be blinded and stored in secure
40
41 263 environments. Only the executive researcher and the head of the department can reach the unblinded
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43 264 informed consents and the key for unblinding. These are stored separately. Digital data will be stored
44 265 pseudonymized in a secure database using Castor EDC (CDISC, Amsterdam, Netherlands). Detailed methods for
45
46 266 data management and storage can be obtained by contacting the corresponding author.

47 48 267 **Authors contribution**

49
50 268 All authors (MV, MK, KvD, HB and FL) were involved in designing this study. MV obtained the approval of the
51
52 269 Medical Ethics Review Committee and drafted the manuscript. Finally, all authors (MV, MK, KvD, HB and FL)
53
54 270 gave feedback on the draft and approved the final manuscript.

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56
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58
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1
2
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5
6

7 276 **Competing interest**

8
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279 Tables

280 *Table 1. Inclusion and Exclusion criteria. When patients have a pacemaker, they cannot use the GrindCare® GC4 (i.e., a*
 281 *portable, single-channel electromyographic recorder to detect sleep bruxism) and will be excluded from that specific part of*
 282 *the study. When patients do not have a smartphone, participants cannot use the BruxApp (i.e., an application on a*
 283 *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

284

285 *Table 2. Questionnaires and clinical data collected as part of the regular care at the hospital, which is used in this*
 286 *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 Emission 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)

287

288 *Table 3. Additional research components, i.e., performed in addition to the regular appointments at the hospital. See*
 289 *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. Bruxoprovoctiontest ⁶¹
	10. Saliva test (Saliva-Check Buffer [®]) ⁶²
Registration	1. BruxApp ⁶¹
	2. GrindCare [®] GC4 ^{32,63}

290

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

Independent variables (categorized)	
1.	Bruxism (<i>when analysing which factors are associated with the presence of TMD pain in patients with PD</i>)
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 (<i>when analysing which factors are associated with the presence of bruxism in patients with PD</i>)
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.

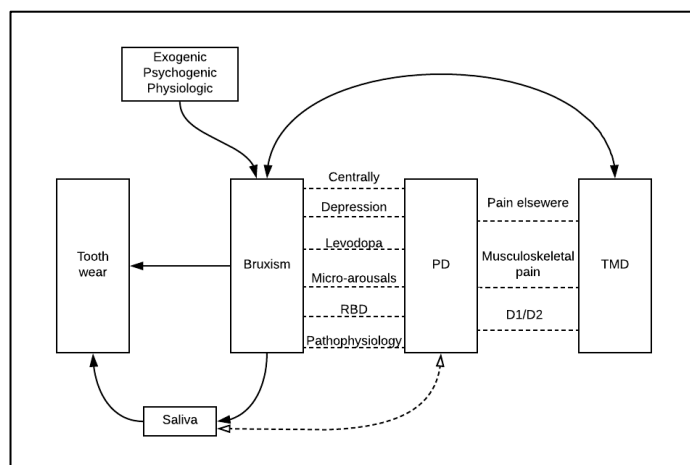


Figure 1. Visualization of the possible interactions between the different research variables. *Parkinson's Disease (PD)* is associated with bruxism through different variables: the dopaminergic system (pathophysiology) plays a role in both conditions; the prodromal phase of PD (RBD) shows the same characteristics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

view only

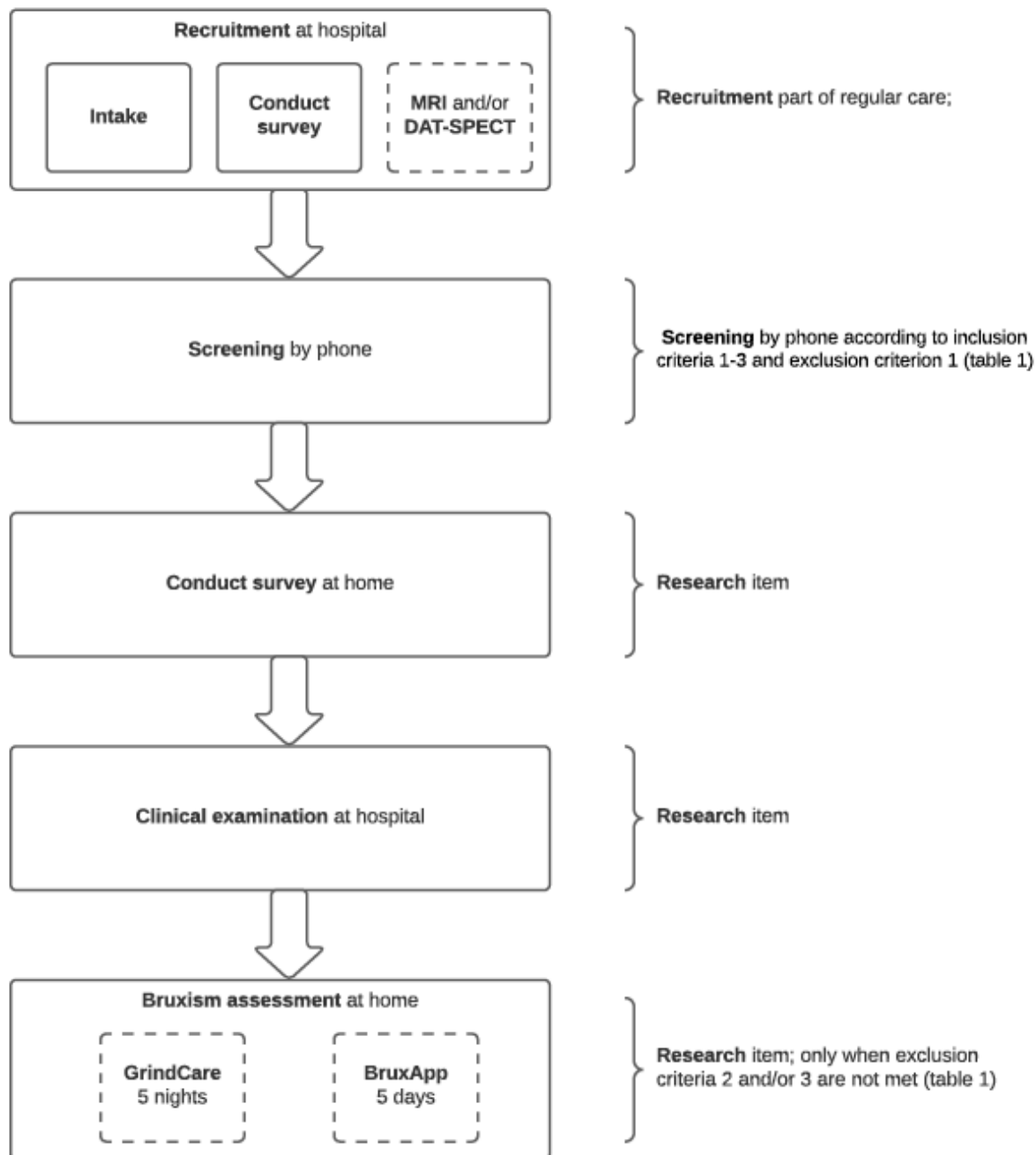


Figure 2. Flowchart of the study in which a distinction was made between the attendance of participants at the hospital and the study components at the participant's home. The intake and first survey is part of the regular care at the hospital, and only followed by an additional MRI and/or DAT-SPECT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

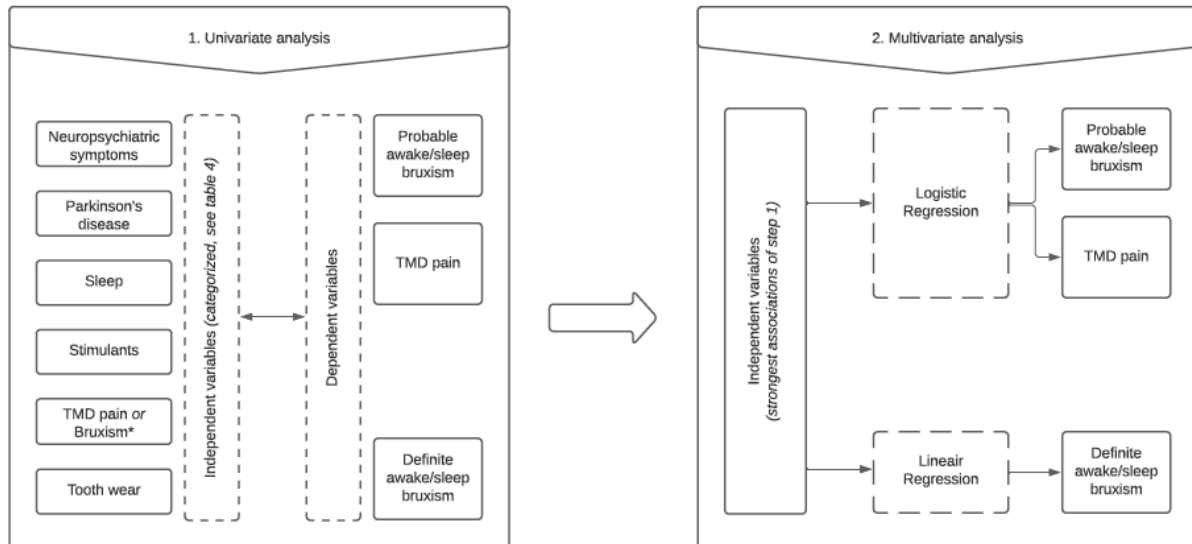


Figure 3. Flowchart of the data-analysis related to the first secondary aim: “to investigate which factors are influencing the presence of probable awake/sleep bruxism, TMD pain and the frequency of definite awake/sleep bruxism”. All variables will be tested individually to see whether an association 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 stage⁴⁷.
- *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 \leq 32)”, “moderate (score 33-58)”, and “severe (score \geq 59)” motor problems⁶⁵.

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 \geq 11 on that subscale)”, “episodic anxiety (score \geq 6 on that subscale)”, “avoidance behavior (score \geq 5 on that subscale)”, and “any anxiety disorder score (score \geq 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-NL⁵⁷ 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 screened⁶². 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 were 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 $\leq 1/3$ (score 2)", "loss of crown height $>1/3$ but $<2/3$ (score 3)" and "loss of crown height $\geq 2/3$ (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 reported²⁵. The prevalence found for these outcome measures were 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 needed⁷⁴. Consequently, 15 events are chosen and thus (4x15=) 60 events are needed. Based on the prevalence of the recent questionnaire-based pilot study²⁵, 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 needed²⁵. For the linear regression, this estimate of the sample size is sufficient to detect medium and large effect sizes⁷⁵. 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	1. Hypersalivation	1. >7.5	1. Abnormal	1. 10-12	1. Normal/high
	2. 0.50-0.25	2. Normal	2. 7.5-6.8	2. Normal	2. 6-9	2. Low
	3. 0.24-0.10	3. Risk	3. 6.7-6.5	3. Risk	3. 0.5	3. Very low
	4. <0.10	4. Pathologic	4. <6.5	4. Pathologic		
During chewing	1. >2.00	1. Hypersalivation	1. >8.0	1. Abnormal	1. 10-12	1. Normal/high
	2. 2.00-0.75	2. Normal	2. 8.0-7.0	2. Normal	2. 6-9	2. Low
	3. 0.74-0.50	3. Risk	3. 6.9-6.5	3. Risk	3. 0-5	3. Very low
	4. <0.50	4. Pathologic	4. <6.5	4. Pathologic		

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 SPIRIT reporting 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

1	Roles and	#5b	Name and contact information for the trial sponsor	7-8
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	7-8
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
22				
23				
24	Introduction			
25				
26				
27	Background and	#6a	Description of research question and justification for undertaking	2-3
28	rationale		the trial, including summary of relevant studies (published and	
29			unpublished) examining benefits and harms for each intervention	
30				
31				
32	Background and	#6b	Explanation for choice of comparators	4
33	rationale: choice of			
34	comparators			
35				
36				
37	Objectives	#7	Specific objectives or hypotheses	3
38				
39				
40	Trial design	#8	Description of trial design including type of trial (eg, parallel	4
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
44				
45				
46	Methods:			
47	Participants,			
48	interventions, and			
49	outcomes			
50				
51				
52				
53	Study setting	#9	Description of study settings (eg, community clinic, academic	4
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
56				
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1	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
2				
3				
4				
5				
6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	n/a
7	description			
8				
9				
10	Interventions:	#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
11	modifications			
12				
13				
14				
15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
16	adherence			
17				
18				
19				
20	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
21	concomitant care			
22				
23				
24	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
25				
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34	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)
35				
36				
37				
38				
39				
40	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
41				
42				
43				
44				
45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4-5
46				
47				
48				
49	Methods: Assignment			
50	of interventions (for			
51	controlled trials)			
52				
53				
54	Allocation: sequence	#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
55	generation			
56				
57				
58				
59				
60				

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

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	5
2	analyses		analyses)	
3				
4	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	5
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
8				
9				
10	Methods: Monitoring			
11				
12	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of	5
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
18				
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22	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	5
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
26				
27	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	4-5
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
31				
32				
33	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	4-5
34			whether the process will be independent from investigators and	
35			the sponsor	
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37				
38	Ethics and			
39	dissemination			
40				
41				
42	Research ethics	#24	Plans for seeking research ethics committee / institutional review	7
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	7
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
50				
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52				
53	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial	4
54			participants or authorised surrogates, and how (see Item 32)	
55				
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1	Consent or assent:	#26b	Additional consent provisions for collection and use of	n/a
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
4				
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6	Confidentiality	#27	How personal information about potential and enrolled	4-5,7
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
9				
10				
11	Declaration of interests	#28	Financial and other competing interests for principal investigators	8
12			for the overall trial and each study site	
13				
14				
15	Data access	#29	Statement of who will have access to the final trial dataset, and	7
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
19				
20	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for	n/a
21	care		compensation to those who suffer harm from trial participation	
22				
23				
24	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results	7
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
29				
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31				
32				
33	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	7,8
34	authorship		professional writers	
35				
36				
37	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	7
38	reproducible research		participant-level dataset, and statistical code	
39				
40				
41	Appendices			
42				
43	Informed consent	#32	Model consent form and other related documentation given to	n/a
44	materials		participants and authorised surrogates	(dutch)
45				
46				
47	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
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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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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:

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3 50 - This observational study will provide accurate data on the presence of painful temporomandibular
4 51 disorders and bruxism in Parkinson patients attending the outpatient clinic for movement disorders of
5 52 Amsterdam UMC, location VUmc, and their possible associated factors like disease severity and
6 53 medication usage.
7
8 54 - Novel information about tooth wear and saliva composition and quantity in patients with Parkinson's
9 55 disease will be collected.
10 56 - Since polysomnographic recordings for the assessment of definite sleep bruxism are not feasible in this
11 57 study, a portable, single-channel electromyographic recorder is used instead.
12 58 - Electromyographic recordings will be performed for several nights in a row, thus taking into account the
13 59 fluctuating nature of sleep bruxism.
14 60 - Because of the design of this study, no causal relationships can be established between the outcome
15 61 variables and predictors.
16 62

63 Introduction

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

69
70 Due to global ageing, the prevalence of PD is estimated to increase significantly in the near future. Ageing is
71 associated with oral health-related issues, which may therefore occur more frequently in the near future as
72 well⁷. Dentists regularly see patients with bruxism in the dental office, which is an oral health-related issue
73 that is not necessarily associated with systemic diseases. Bruxism is currently defined as "a repetitive jaw-
74 muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the
75 mandible"⁸. It can occur during sleep, indicated as sleep bruxism, or during wakefulness, indicated as awake
76 bruxism⁸. Not only bruxism itself, but also its possible consequences, such as mechanical tooth wear and
77 temporomandibular disorders (TMD), have hardly been studied in patients with PD. TMD is a collective term
78 embracing disorders of the temporomandibular joint, masticatory muscles, and adjacent anatomical
79 structures⁹. TMD can present as painful and non-painful conditions. Patients with TMD can report, for
80 example, orofacial pain (including headache), limitations in the movement of the mandible, and joint noises⁹.
81 Both tooth wear and TMD may affect the oral health-related quality of life¹⁰.

82
83 In a population with PD patients, oral health was recently studied¹¹. It was shown that the oral health in PD
84 patients is deteriorated as compared to their peers without PD. Besides, medication usage can influence
85 salivation production, which in turn influences the oral environment¹². Also, gastrointestinal problems are
86 more frequently shown in patients with PD. In turn, this could influence the presence of tooth wear due to
87 reflux^{13,14}.

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3 89 While oral health in PD has not been studied widely¹¹, oral (dys-)function in PD has been studied even less,
4 90 even though PD, bruxism, and TMD have been suggested to share several common characteristics (see Figure
5 91 1). Similar to PD, bruxism is a condition that is considered to be regulated centrally and not peripherally¹⁵. In
6 92 addition, in the pathophysiology of both PD and bruxism, the brain dopamine system plays an important role<sup>16-
7 93 18</sup>. Besides, sleep disturbances¹⁹ that are present both in PD²⁰ and in sleep bruxism, are associated with arousal
8 94 activity^{19,21}. As a result of such arousal activity, sleep bruxism may occur more frequently in people with sleep
9 95 disturbances than in those without²¹. Also, in the prodromal phase of PD, a higher rhythmic masticatory
10 96 muscle activity (RMMA) on polysomnography in NREM sleep has been observed, compared to controls²². This
11 97 is a characteristic that is also seen in sleep bruxism patients²³. Furthermore, bruxism may be considered as a
12 98 risk factor for TMD, depending on the assessment methods used²⁴. TMD itself shares some characteristics with
13 99 PD. For example, musculoskeletal pain (of which TMD pain is a subtype) is frequently reported by patients with
14 100 PD^{3,25}. Finally, suggestions have been put forward that alterations in the dopaminergic system are also present
15 101 in patients with pain in the orofacial region²⁶, although this remains to be confirmed in patients with TMD
16 102 pain.

17 103
18 104 Recently, a questionnaire-based pilot study in 368 patients with PD and 340 controls suggested a higher
19 105 prevalence of bruxism and TMD pain in patients with PD²⁷. Also, PD patients reported a higher mean TMD-pain
20 106 intensity than controls²⁷. Besides, a large Taiwanese study showed a two-fold increased risk of TMD in patients
21 107 with PD as compared to controls²⁸. However, because of the limitations of the described studies (e.g.,
22 108 questionnaire-based study²⁷; no international validated clinical examination used; no detailed explanation of
23 109 the clinical examination given; and only newly diagnosed TMD-patients included)²⁸, extrapolation of these
24 110 findings requires further verification through clinical and instrumental data. Hence, to overcome some of the
25 111 limitations, the present protocol was designed. The planned study will acquire more objective clinical and
26 112 instrumental measures for awake and sleep bruxism and TMD pain, which can give more valid information on
27 113 outcomes like the presence of bruxism in this population. Also, additional factors, such as the severity of PD
28 114 and cognitive function, will be included as possible predictors for bruxism and/or TMD pain in PD patients.
29 115 Knowledge of the factors that can influence bruxism and/or TMD pain in patients with PD will help dentists
30 116 and other oral health care providers to provide individualised care to prevent and/or alleviate symptoms of
31 117 bruxism and/or TMD pain and their consequences in this vulnerable group of patients.

32 118
33 119 Based on the above-summarized evidence, the primary aim of this study is to investigate the presence of
34 120 bruxism and TMD pain in PD patients, through objective clinical and instrumental measurements. Based on our
35 121 pilot-study outcomes²⁷, we hypothesise that the prevalence of bruxism and TMD pain in the current
36 122 population will be higher than in their peers without PD, as described in the literature^{29,30}.

37 123
38 124 In addition, the secondary aims and their corresponding hypotheses are the following:

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3 125 1. To identify which factors are associated with bruxism and TMD pain in PD patients. We hypothesise that
4 126 factors like medication usage¹⁶, disease severity^{15,17}, psychosocial factors³¹⁻³³, and lifestyle factors^{31,32,34} are
5 127 influencing the studied associations.
6
7 128 2. To investigate whether the salivary flow, the pH, and the buffer capacity of saliva in patients with PD are
8 129 related to the severity of tooth wear. Our hypothesis is that in patients with PD, the saliva composition
9 130 and salivary flow deviate from normal standards and that this is associated with the severity of tooth
10 131 wear¹⁴.
11
12 132 3. To investigate with Dopamine Transporter Single Photon Emission Computed Tomography (DAT-SPECT)
13 133 whether there is a relationship between the degree of presynaptic dopaminergic loss and the presence of
14 134 bruxism in these patients. The hypothesis is that there is a difference in striatal dopaminergic deficit
15 135 between PD patients with and without bruxism, in which patients without bruxism show a smaller deficit.
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137 **Methods and analysis**

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

143 **Participants and eligibility**

144 Patients already clinically diagnosed with PD or planned for an intake appointment with presumable PD at the
 145 outpatient clinic for movement disorders of the VUmc, will be eligible to participate in the study. Yearly, about
 146 100-120 new consultations for PD are seen in the outpatient clinic. In addition, patients already receiving
 147 treatment at the VUmc are eligible for participation as well. The inclusion and exclusion criteria are listed in
 148 Table 1.

150 *Table 1. Inclusion and Exclusion criteria. When patients have a pacemaker, they cannot use the GrindCare® GC4 (i.e., a
 151 portable, single-channel electromyographic recorder to detect sleep bruxism) and will be excluded from that specific part of
 152 the study. When patients do not have a smartphone, participants cannot use the BruxApp (i.e., an application on a
 153 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

155 **Study procedure**

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

165 *Table 2. Questionnaires and clinical data collected as part of the regular care at the hospital, which is used in this
 166 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 Emission 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)

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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}

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Main study parameters

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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 assessment⁸. According to international consensus, a classification of the probability that bruxism is present can be made as follows: possible, probable, and definite bruxism presence⁸. In this research, all probabilities of bruxism presence can be determined, however, the highest probability will be used (viz., both

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3 180 probable and definite). When patients cannot use the GrindCare® GC4 and/or BruxApp, and more certainty
4 181 towards a definite presence is thus impossible, probable bruxism presence will be determined with the use of
5 182 data from the clinical examination, based on the presence of positive symptoms of bruxism (viz., clenching
6 183 marks in the soft tissues of the cheek, tongue, or lip, mechanical tooth wear (attrition), and/or hypertrophy of
7 184 the masseter muscle)⁸.

11 185 The TMD-pain diagnosis will be established according to the Diagnostic Criteria for TMD (DC/TMD)⁵⁰, with the
12 186 use of standardized questionnaires and clinical examination procedures. Based on the collected data, the
13 187 following diagnoses can be set: myalgia (local myalgia, myofascial pain, myofascial pain with referral),
14 188 arthralgia, headache attributed to TMD, and non-painful joint disorders (disc displacement with reduction, disc
15 189 displacement with reduction with intermitted locking, disc displacement without reduction with limited mouth
16 190 opening, disc displacement without reduction without limited mouth opening, degenerative joint disease,
17 191 subluxation). The main focus of this research protocol will be the TMD-pain diagnosis, for the establishment of
18 192 which the diagnostic flow chart of the DC/TMD will be used⁵⁰.

193 **Secondary study parameters**

194 To identify which factors are associated with bruxism and TMD pain in PD patients, several variables will be
195 evaluated (see Tables 2 and 3), using different clinical/instrumental measures (see appendix 1-3). Most of
196 these variables have already been reported as possible risk factors for bruxism³² and/or TMD⁶¹ in the general
197 population³¹⁻³³. However, the variables dopaminergic medication usage and disease stage/severity of PD have
198 not been studied yet in the association with bruxism or TMD pain in PD patients. Finally, if DAT-SPECT imaging
199 is available, we will compare the measured presynaptic striatal dopaminergic deficit between participants with
200 and without bruxism⁴⁶.

202 **Sample size**

203 According the pilot study, the prevalence of awake bruxism, sleep bruxism, and TMD pain in patients with PD is
204 46%, 24%, and 29.5%, respectively²³. Taking the cautious approach, we calculated the sample size for all
205 conditions and chose the largest sample size. Aiming for a precision of 5% with a level of confidence of 95%,
206 246 participants are needed⁶². See appendix 2 for the sample size calculation. Furthermore, the approach to
207 calculate the sample size for the most important secondary aim (viz., to identify which factors are associated
208 with bruxism and TMD pain in PD patients) is also shown in appendix 2. The numbers are obtained when
209 reaching the sample size for the primary aim.

211 **Statistical approach**

212 With the use of descriptive tests, demographic data will be summarised. In Figure 3, it is shown how the
213 dataset is analysed to give an answer on which factor is associated with the presence/absence of probable
214 bruxism/TMD pain or with the frequency (i.e., the number of bruxism events per hour) of definite bruxism. The
215 forward selection procedure will be used for the (strongest) independent variables (see Table 4) until all
216 variables in this regression model show a P-value <0.05 (See Step 2, Figure 3). Finally, to analyse if there is an

217 association between tooth wear and composition of saliva, Spearman's correlation coefficient will be used. For
 218 the DAT-SPECT, a semi-quantitative analysis will be used. Ratios for specific versus non-specific binding will be
 219 calculated for the regions of interest (viz., left and right putamen and caudate nucleus, using the occipital
 220 cortex as a reference area) and analysed using the independent sample t-test^{46,47}.

221

222 *Table 4. The independent variables (categorized) that will be investigated for one of the secondary aims: which factors are*
 223 *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)

224

225 Patient and public involvement

226 Neither patients nor the community were involved in the design or performance of this study. However,
 227 feedback from participants of the earlier pilot study²³ was used to design this study. The burden for the
 228 participants will be kept as minimal as possible. On request, the outcomes of this study will be disseminated to
 229 the participants.

230 Discussion

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

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238 To the best of our knowledge, this is the first study that attempts to objectively measure the presence of
 239 awake bruxism, sleep bruxism, and TMD pain in a population of patients with PD. Previous studies investigated
 240 the prevalence of awake bruxism in this population, however only few participants were included or only
 241 questionnaires were used^{23,63}. When quantifying bruxism with continuous data, recent insights showed a
 242 better quality of a definite bruxism diagnosis⁸. Nevertheless, we used a dichotomous outcome in this protocol
 243 study to answer our first aim, i.e., to investigate the presence of bruxism. Besides, we also included self-report
 244 and clinical data, which do not yield continuous outcomes. Despite this, in the present study, the use of the
 245 GrindCare[®] GC4 and the BruxApp can give more certainty towards a definite establishment of sleep and awake
 246 bruxism, respectively⁸. This enables the analysis of continuous outcomes, which has been suggested by several

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3 247 authors^{64,65}. However, as mentioned earlier, not every participant will be able to use the GrindCare® GC4
4 248 and/or the Bruxapp. Therefore, this protocol is designed to include all probability levels for the assessment of
5
6 249 bruxism, which contributes to the feasibility of this protocol⁸. In addition, the clinical examination according
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8 250 to the DC/TMD⁵⁰ enables setting a valid TMD-pain diagnosis, making a distinction between several TMD
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10 251 complaints, and comparing the outcomes with other (inter-) national research.

11 252
12 253 Because PD patients are vulnerable and burdened with frequent visits to multiple caregivers (e.g., their
13
14 254 neurologist, physiotherapist, and speech therapist), it is important to burden the participants as minimally as
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16 255 possible. Therefore, during the process of designing this study and collecting the data, a multidisciplinary
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18 256 approach was established between neurologists and dentists to enable an as efficient as possible usage of the
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20 257 patient's time and energy.

21 258
22 259 The targeted number of inclusions will be a challenge. However, the calculated sample size is an estimation,
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24 260 because no clinical prevalences are known as yet. Like in otherwise healthy individuals, clenching and grinding
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26 261 are not always recognized by the patients themselves^{66,67}, thus the prevalence of sleep bruxism in the pilot
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28 262 study could have been underestimated. This means that the calculated sample size in this study might be
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30 263 higher than eventually required. Therefore, an interim analysis will be performed after 130 included
31
32 264 participants or 6 months.

33 265
34 266 This study has no longitudinal character and therefore, no causal relations can be observed between the (in-
35
36 267 dependent variables. Also, polysomnography is the golden standard to detect sleep bruxism while in the
37
38 268 present study, a portable electromyographic recorder will be used⁸. However, since this device will be used for
39
40 269 several nights in a row, the fluctuating character of sleep bruxism can be taken into account and is therefore
41
42 270 considered a good proxy for definite sleep bruxism⁵⁹. It should be noted, however, that the portable recorder
43
44 271 will fail to enable a distinction between jaw-muscle activities related to sleep bruxism and those related to
45
46 272 other orofacial movement disorders like oral dyskinesia and oro-mandibular dystonia⁶⁸. This is an important
47
48 273 issue, because such movement disorders can be present in patients with PD related to their medication usage.
49
50 274 Fortunately, in the questionnaire and clinical examination of the MDS-UPDRS³⁹ (Table 2), the presence of oral
51
52 275 dyskinesia and oro-mandibular dystonia is included. Hence, it is possible to correct for their presence in the
53
54 276 data analysis.

55 277
56 278 In conclusion, this study will give more detailed information about the presence of bruxism and TMD pain in
57
58 279 patients with PD, as well as about possible associated factors like medication usage and severity of the disease.
59
60 280 Finally, more clinically relevant information will become available for dentists and other oral health care
281
282 281 professionals about the amount of tooth wear and the composition of saliva in patients with PD.

282 **Ethics and dissemination:**

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

288
289 Due to the sensitive nature of personal information, all data will be blinded and stored in secure
290 environments. Only the executive researcher and the head of the department can reach the unblinded
291 informed consents and the key for unblinding. These are stored separately. Digital data will be stored
292 pseudonymized in a secure database using Castor EDC (CDISC, Amsterdam, Netherlands). Detailed methods for
293 data management and storage can be obtained by contacting the corresponding author.

294 **Authors contribution**

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

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303 **Competing interest**

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Figure Legends

27
28 Figure 1. Visualization of the possible interactions between the different research variables. *Parkinson's Disease (PD)* is
29 associated with bruxism through different variables: the dopaminergic system (pathophysiology) plays a role in both
30 conditions; the prodromal phase of PD (RBD) shows the same characteristics during sleep as does bruxism; sleep
31 disturbances lead to micro-arousals that can lead to bruxism; dopaminergic medication (levodopa) can influence bruxism;
32 depression is one of the risk factors for bruxism and is more prevalent in patients with PD; and finally, both PD and bruxism
33 are regulated centrally and not peripherally. PD is also associated with TMD: PD patients experience pain in the entire body
34 (i.e., widespread pain), which is a risk factor for TMD pain; also, musculoskeletal pain (as in TMD pain) is frequently present;
35 and finally, alterations in the striatal dopaminergic system (D1/D2 ratio) could play a role in TMD pain. Bruxism itself is a
36 risk factor for TMD pain and vice versa. Besides, tooth wear can be a consequence of bruxism. When bruxism occurs, saliva
37 can be increased, which can be a protective factor for tooth wear. Also, saliva can be changed due to PD medication.
38 Finally, several exogenic, psychogenic, and physiologic factors can be a risk for bruxism.

41
42 Figure 2. Flowchart of the study in which a distinction was made between the attendance of participants at the hospital and
43 the study components at the participant's home. The intake and first survey is part of the regular care at the hospital, and
44 only followed by an additional MRI and/or DAT-SPECT scan when indicated (dashed line). When patients are eligible and
45 consent to participate (screening by phone), the additional data are collected after the intake. First, a questionnaire is filled
46 in by the participants. After that, the participant is invited for the clinical examination. When questionnaires/screenings
47 that are part of the regular care were filled in ≥ 1 year ago, participants will be asked to repeat this procedure
48 simultaneously with the additional questionnaire and/or clinical examination. Finally, participants will sleep for 5 complete
49 registration nights with the GrindCare for the assessment of sleep bruxism (when exclusion criterion 2 was not met) and use
50 the BruxApp for 5 complete registration days for the assessment of awake bruxism (when exclusion criterion 3 was not
51 met).

57
58 Figure 3. Flowchart of the data-analysis related to the first secondary aim: "to investigate which factors are influencing the
59 presence of probable awake/sleep bruxism, TMD pain and the frequency of definite awake/sleep bruxism". All variables will
60 be tested individually to see whether an association with the dependent variable (awake and sleep bruxism and TMD pain)

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2
3 *exists, and to see how strong this association is (step 1). This dataset will be analysed for both probable bruxism and TMD*
4 *pain with the use of logistic regression analyses. For definite bruxism, a linear regression analysis will be used (step 2). The*
5 *forward selection procedure will be used for the (strongest) independent variables until all variables in this regression model*
6 *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.*
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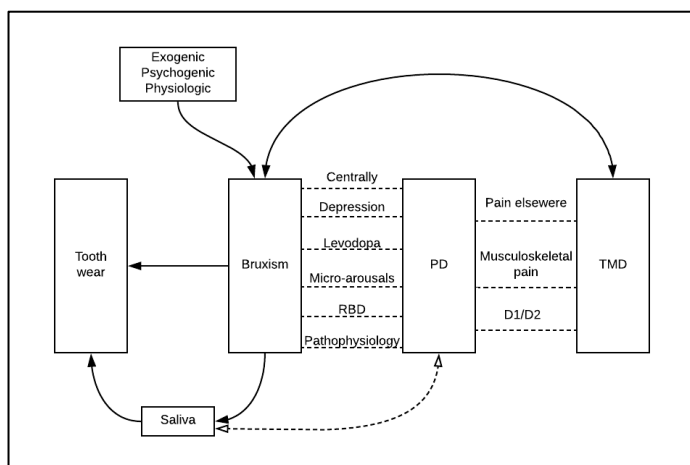


Figure 1. Visualization of the possible interactions between the different research variables. *Parkinson's Disease (PD)* is associated with bruxism through different variables: the dopaminergic system (pathophysiology) plays a role in both conditions; the prodromal phase of PD (RBD) shows the same characteristics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

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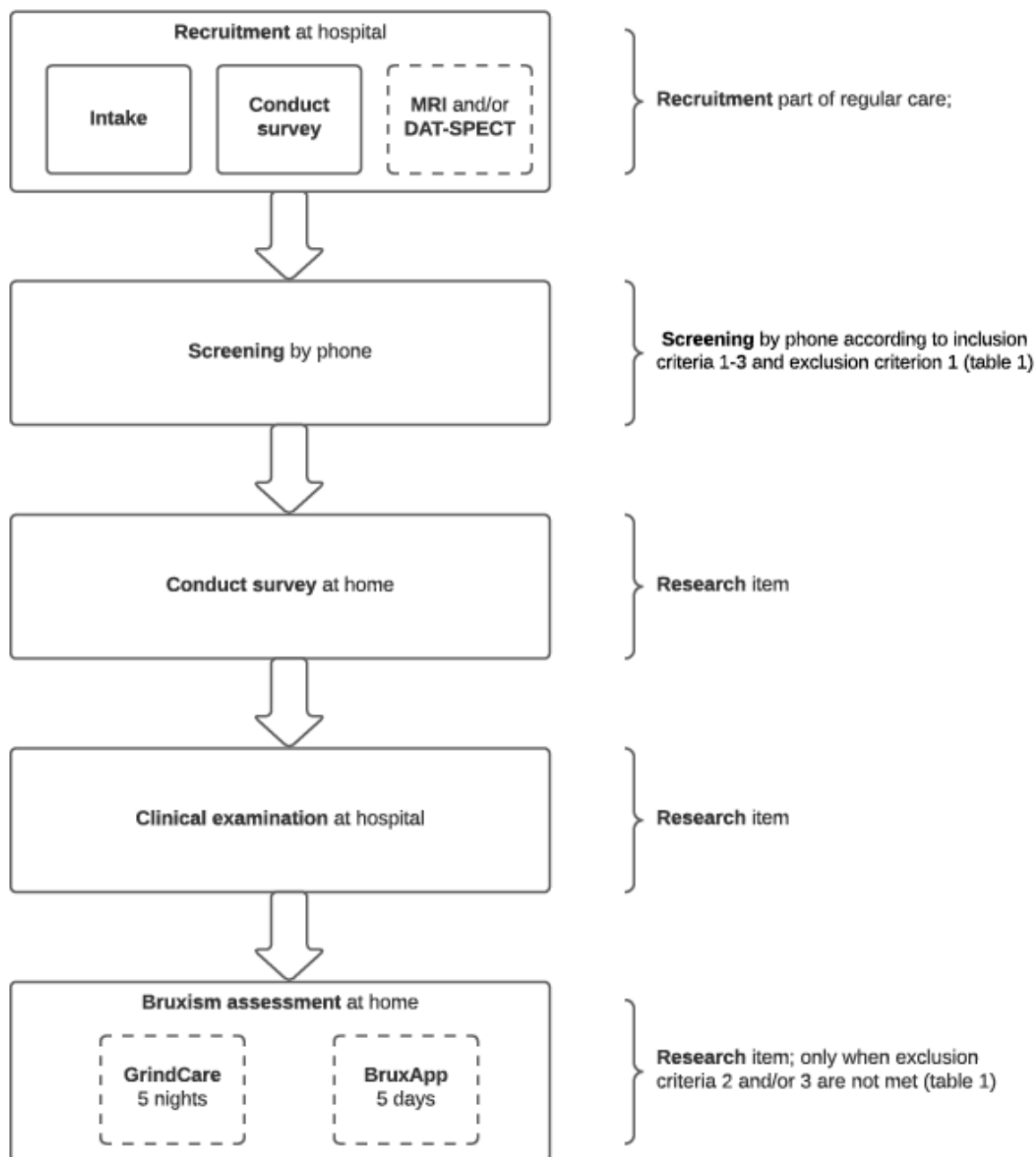


Figure 2. Flowchart of the study in which a distinction was made between the attendance of participants at the hospital and the study components at the participant's home. The intake and first survey is part of the regular care at the hospital, and only followed by an additional MRI and/or DAT-SPECT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

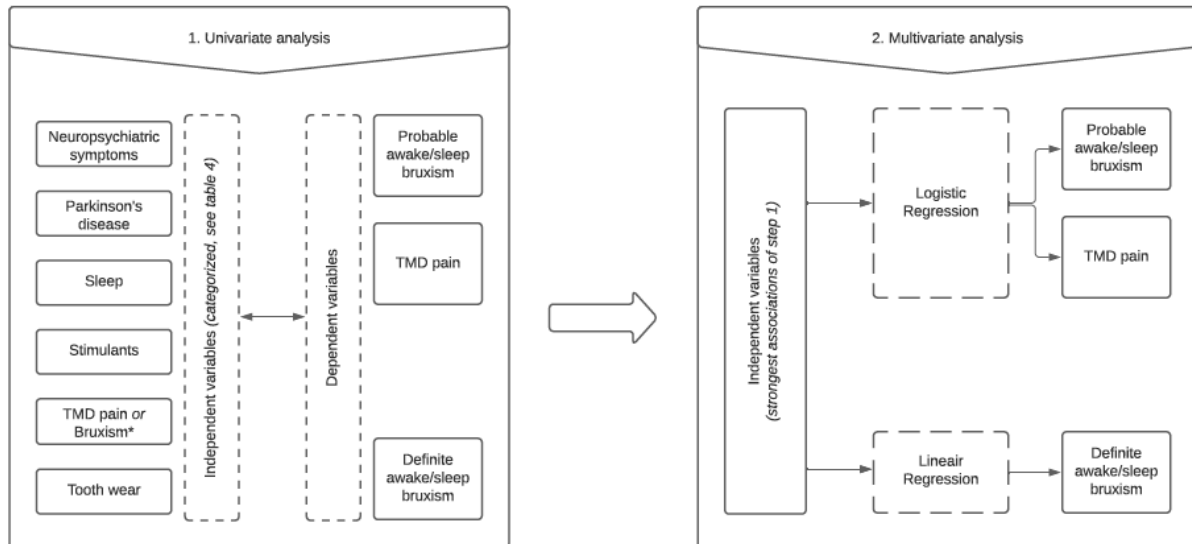


Figure 3. Flowchart of the data-analysis related to the first secondary aim: “to investigate which factors are influencing the presence of probable awake/sleep bruxism, TMD pain and the frequency of definite awake/sleep bruxism”. All variables will be tested individually to see whether an association 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 stage¹.
- 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 \leq 32)”, “moderate (score 33-58)”, and “severe (score \geq 59)” motor problems⁵.

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 \geq 11 on that subscale)”, “episodic anxiety (score \geq 6 on that subscale)”, “avoidance behavior (score \geq 5 on that subscale)”, and “any anxiety disorder score (score \geq 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-NL¹⁷ 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 screened²⁰. 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 $\leq 1/3$ (score 2)", "loss of crown height $>1/3$ but $<2/3$ (score 3)" and "loss of crown height $\geq 2/3$ (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 reported²⁶. The prevalence found for these outcome measures were 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 needed²⁷. Consequently, 15 events are chosen and thus (4x15=) 60 events are needed. Based on the prevalence of the recent questionnaire-based pilot study²⁶, 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 needed²⁶. For the linear regression, this estimate of the sample size is sufficient to detect medium and large effect sizes²⁸. 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.

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

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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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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:

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3 50 - This observational study will provide accurate data on the presence of painful temporomandibular
4 51 disorders and bruxism in Parkinson patients attending the outpatient clinic for movement disorders of
5 52 Amsterdam UMC, location VUmc, and their possible associated factors like disease severity and
6 53 medication usage.
7 54 - Novel information about tooth wear and saliva composition and quantity in patients with Parkinson's
8 55 disease will be collected.
9 56 - Since polysomnographic recordings for the assessment of definite sleep bruxism are not feasible in this
10 57 study, a portable, single-channel electromyographic recorder is used instead.
11 58 - Electromyographic recordings will be performed for several nights in a row, thus taking into account the
12 59 fluctuating nature of sleep bruxism.
13 60 - Because of the absence of a control group, no direct comparisons between individuals with PD and similar
14 61 individuals without PD can be made.
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63 Introduction

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

69
70 Due to global ageing, the prevalence of PD is estimated to increase significantly in the near future. Ageing is
71 associated with oral health-related issues, which may therefore occur more frequently in the near future as
72 well⁷. Dentists regularly see patients with bruxism in the dental office, which is an oral health-related issue
73 that is not necessarily associated with systemic diseases. Bruxism is currently defined as "a repetitive jaw-
74 muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the
75 mandible"⁸. It can occur during sleep, indicated as sleep bruxism, or during wakefulness, indicated as awake
76 bruxism⁸. Not only bruxism itself, but also its possible consequences, such as mechanical tooth wear and
77 temporomandibular disorders (TMD), have hardly been studied in patients with PD. TMD is a collective term
78 embracing disorders of the temporomandibular joint, masticatory muscles, and adjacent anatomical
79 structures⁹. TMD can present as painful and non-painful conditions. Patients with TMD can report, for
80 example, orofacial pain (including headache), limitations in the movement of the mandible, and joint noises⁹.
81 Both tooth wear and TMD may affect the oral health-related quality of life¹⁰.

82
83 In a population with PD patients, oral health was recently studied¹¹. It was shown that the oral health in PD
84 patients is deteriorated as compared to their peers without PD. Besides, medication usage can influence
85 salivation production, which in turn influences the oral environment¹². Also, gastrointestinal problems are
86 more frequently shown in patients with PD. In turn, this could influence the presence of tooth wear due to
87 reflux^{13,14}.

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3 89 While oral health in PD has not been studied widely¹¹, oral (dys-)function in PD has been studied even less,
4 90 even though PD, bruxism, and TMD have been suggested to share several common characteristics (see Figure
5 91 1). Similar to PD, bruxism is considered to be regulated centrally and not peripherally¹⁵. In addition, in the
6 92 pathophysiology of both PD and bruxism, the brain dopamine system plays an important role¹⁶⁻¹⁸. Besides,
7 93 sleep disturbances¹⁹ that are present both in PD²⁰ and in sleep bruxism, are associated with arousal
8 94 activity^{19,21}. As a result of such arousal activity, sleep bruxism may occur more frequently in people with sleep
9 95 disturbances than in those without²¹. Also, in the prodromal phase of PD, a higher rhythmic masticatory
10 96 muscle activity (RMMA) on polysomnography in NREM sleep has been observed, compared to controls²². This
11 97 is a characteristic that is also seen in sleep bruxism patients²³. Furthermore, bruxism may be considered as a
12 98 risk factor for TMD, depending on the assessment methods used²⁴. TMD itself shares some characteristics with
13 99 PD. For example, musculoskeletal pain (of which TMD pain is a subtype) is frequently reported by patients with
14 100 PD^{3,25}. Finally, suggestions have been put forward that alterations in the dopaminergic system are also present
15 101 in patients with pain in the orofacial region²⁶, although this remains to be confirmed in patients with TMD
16 102 pain.

17 103
18 104 Recently, a questionnaire-based pilot study in 368 patients with PD and 340 controls suggested a higher
19 105 prevalence of bruxism and TMD pain in patients with PD²⁷. Also, PD patients reported a higher mean TMD-pain
20 106 intensity than controls²⁷. Besides, a large Taiwanese study showed a two-fold increased risk of TMD in patients
21 107 with PD as compared to controls²⁸. However, because of the limitations of the described studies (e.g.,
22 108 questionnaire-based study²⁷; no international validated clinical examination used; no detailed explanation of
23 109 the clinical examination given; and only newly diagnosed TMD-patients included)²⁸, extrapolation of these
24 110 findings requires further verification through clinical and instrumental data. Hence, to overcome some of the
25 111 limitations, the present protocol was designed. The planned study will acquire more objective clinical and
26 112 instrumental measures for awake and sleep bruxism and TMD pain, which can give more valid information on
27 113 outcomes like the presence of bruxism in this population. Also, additional factors, such as the severity of PD
28 114 and cognitive function, will be included as possible predictors for bruxism and/or TMD pain in PD patients.
29 115 Knowledge of the factors that can influence bruxism and/or TMD pain in patients with PD will help dentists
30 116 and other oral health care providers to provide individualised care to prevent and/or alleviate symptoms of
31 117 bruxism and/or TMD pain and their consequences in this vulnerable group of patients.

32 118
33 119 Based on the above-summarized evidence, the primary aim of this study is to investigate the presence of
34 120 bruxism and TMD pain in PD patients, through objective clinical and instrumental measurements. Based on our
35 121 pilot-study outcomes²⁷, we hypothesise that the prevalence of bruxism and TMD pain in the current
36 122 population will be higher than in their peers without PD, as described in the literature^{29,30}.

37 123
38 124 In addition, the secondary aims and their corresponding hypotheses are the following:

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3 125 1. To identify which factors are associated with bruxism and TMD pain in PD patients. We hypothesise that
4 126 factors like medication usage¹⁶, disease severity^{15,17}, psychosocial factors³¹⁻³³, and lifestyle factors^{31,32,34} are
5 127 influencing the studied associations.
6
7 128 2. To investigate whether the salivary flow, the pH, and the buffer capacity of saliva in patients with PD are
8 129 related to the severity of tooth wear. Our hypothesis is that in patients with PD, the saliva composition
9 130 and salivary flow deviate from normal standards and that this is associated with the severity of tooth
10 131 wear¹⁴.
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12 132 3. To investigate with Dopamine Transporter Single Photon Emission Computed Tomography (DAT-SPECT)
13 133 whether there is a relationship between the degree of presynaptic dopaminergic loss and the presence of
14 134 bruxism in these patients. The hypothesis is that there is a difference in striatal dopaminergic deficit
15 135 between PD patients with and without bruxism, in which patients without bruxism show a smaller deficit.
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137 **Methods and analysis**

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

143 **Participants and eligibility**

144 Patients already clinically diagnosed with PD or planned for an intake appointment with presumable PD at the
 145 outpatient clinic for movement disorders of the VUmc, will be eligible to participate in the study. Yearly, about
 146 100-120 new consultations for PD are seen in the outpatient clinic. In addition, patients already receiving
 147 treatment at the VUmc are eligible for participation as well. The inclusion and exclusion criteria are listed in
 148 Table 1.

150 *Table 1. Inclusion and Exclusion criteria. When patients have a pacemaker, they cannot use the GrindCare® GC4 (i.e., a
 151 portable, single-channel electromyographic recorder to detect sleep bruxism) and will be excluded from that specific part of
 152 the study. When patients do not have a smartphone, participants cannot use the BruxApp (i.e., an application on a
 153 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

155 **Study procedure**

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

165 *Table 2. Questionnaires and clinical data collected as part of the regular care at the hospital, which is used in this
 166 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 Emission 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)

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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}

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Main study parameters

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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 assessment⁸. According to international consensus, a classification of the probability that bruxism is present can be made as follows: possible, probable, and definite bruxism presence⁶¹. In this research, all probabilities of bruxism presence can be determined, however, the highest probability will be used (viz., both

180 probable and definite). When patients cannot use the GrindCare® GC4 and/or BruxApp, and more certainty
181 towards a definite presence is thus impossible, probable bruxism presence will be determined with the use of
182 data from the clinical examination, based on the presence of positive symptoms of bruxism (viz., clenching
183 marks in the soft tissues of the cheek, tongue, or lip, mechanical tooth wear (attrition), and/or hypertrophy of
184 the masseter muscle)⁶¹. Differences in PD symptoms between those who can, and those who cannot complete
185 the instrumental assessments will be tested as to gain insight into the external validity or generalizability of
186 the conclusions involving bruxism modeling.

187 The TMD-pain diagnosis will be established according to the Diagnostic Criteria for TMD (DC/TMD)⁵⁰, with the
188 use of standardized questionnaires and clinical examination procedures. Based on the collected data, the
189 following diagnoses can be set: myalgia (local myalgia, myofascial pain, myofascial pain with referral),
190 arthralgia, headache attributed to TMD, and non-painful joint disorders (disc displacement with reduction, disc
191 displacement with reduction with intermitted locking, disc displacement without reduction with limited mouth
192 opening, disc displacement without reduction without limited mouth opening, degenerative joint disease,
193 subluxation). The main focus of this research protocol will be the TMD-pain diagnosis, for the establishment of
194 which the diagnostic flow chart of the DC/TMD will be used⁵⁰.

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

197

198 **Secondary study parameters**

199 To identify which factors are associated with bruxism and TMD pain in PD patients, several variables will be
200 evaluated (see Tables 2 and 3), using different clinical/instrumental measures (see appendix 1-3). Most of
201 these variables have already been reported as possible risk factors for bruxism³² and/or TMD⁶² in the general
202 population³¹⁻³³. However, the variables dopaminergic medication usage and disease stage/severity of PD have
203 not been studied yet in the association with bruxism or TMD pain in PD patients. Finally, if DAT-SPECT imaging
204 is available, we will compare the measured presynaptic striatal dopaminergic deficit between participants with
205 and without bruxism⁴⁶.

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207 **Sample size**

208 According the pilot study, the prevalence of awake bruxism, sleep bruxism, and TMD pain in patients with PD is
209 46%, 24%, and 29.5%, respectively²³. Taking the cautious approach, we calculated the sample size for awake
210 bruxism, sleep bruxism, and TMD pain and chose the largest sample size. Aiming for a precision of 5% with a
211 level of confidence of 95%, 246 participants are needed⁶³. See appendix 2 for the sample size calculation.
212 Furthermore, the approach to calculate the sample size for the most important secondary aim (viz., to identify
213 which factors are associated with bruxism and TMD pain in PD patients) is also shown in appendix 2. The
214 numbers are obtained when reaching the sample size for the primary aim.

215

216 **Statistical approach**

217 With the use of descriptive tests, demographic data will be summarised. In Figure 3, it is shown how the
 218 dataset is analysed to give an answer on which factor is associated with the presence/absence of probable
 219 bruxism/TMD pain or with the frequency (i.e., the number of bruxism events per hour) of definite bruxism. The
 220 forward selection procedure will be used for the (strongest) independent variables (see Table 4) until all
 221 variables in this regression model show a P-value <0.05 (See Step 2, Figure 3). Finally, to analyse if there is an
 222 association between tooth wear and composition of saliva, Spearman's correlation coefficient will be used. For
 223 the DAT-SPECT, a semi-quantitative analysis will be used. Ratios for specific versus non-specific binding will be
 224 calculated for the regions of interest (viz., left and right putamen and caudate nucleus, using the occipital
 225 cortex as a reference area) and analysed using the independent sample t-test^{46,47}.

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227 *Table 4. The independent variables (categorized) that will be investigated for one of the secondary aims: which factors are*
 228 *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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230 Patient and public involvement

231 Neither patients nor the community were involved in the design of this study. However, feedback from
 232 participants of the earlier pilot study²³ was used to design this study. Patients with PD will be involved in the
 233 performance of the study. The burden for the participants will be kept as minimal as possible. On request, the
 234 outcomes of this study will be disseminated to the participants.

235 Discussion

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

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243 To the best of our knowledge, this is the first study that attempts to objectively measure the presence of
 244 awake bruxism, sleep bruxism, and TMD pain in a population of patients with PD. Previous studies investigated
 245 the prevalence of awake bruxism in this population, however only few participants were included or only
 246 questionnaires were used^{23,64}. When quantifying bruxism with continuous data, recent insights showed a

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3 247 better quality of a definite bruxism diagnosis⁶¹. Nevertheless, we used a dichotomous outcome in this protocol
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5 248 study to answer our first aim, i.e., to investigate the presence of bruxism. Besides, we also included self-report
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7 249 and clinical data, which do not yield continuous outcomes. Despite this, in the present study, the use of the
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9 250 GrindCare® GC4 and the BruxApp can give more certainty towards a definite establishment of sleep and awake
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11 251 bruxism, respectively⁶¹. This enables the analysis of continuous outcomes, which has been suggested by
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13 252 several authors^{65,66}. However, as mentioned earlier, not every participant will be able to use the GrindCare®
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15 253 GC4 and/or the Bruxapp. Therefore, this protocol is designed to include all probability levels for the
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17 254 assessment of bruxism, which contributes to the feasibility of this protocol⁶¹. Importantly, participants able to
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19 255 complete all assessments may differ from those who cannot complete instrumental assessments due to
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21 256 differences in severity of their PD symptoms. Fine motor problems which occur in PD create barriers for
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23 257 electrode placement and cell phone use as required for instrumental assessments of sleep and awake bruxism.
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25 258 Therefore, we will test for PD symptom differences between subgroups defined by comparing participants
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27 259 completing or not completing instrumental assessments. If differences are found, this will indicate limitations
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29 260 to the external validity or generalizability of conclusions involving bruxism modeling.
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33 262 In addition, the clinical examination according to the DC/TMD⁵⁰ enables setting a valid TMD-pain diagnosis,
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35 263 making a distinction between several TMD complaints, and comparing the outcomes with other (inter-)
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37 264 national research. An important aspect of a TMD-pain diagnosis according to the DC/TMD is that it considers
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39 265 the aspect of “familiar pain” as part of the diagnostic algorithm. As such, PD-related pain characteristics like
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41 266 pain exacerbation due to “wearing off” of dopaminergic medication and lower pain thresholds in individuals
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43 267 living with PD as compared to similar individuals without PD⁶⁷, will be taken into account.
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47 269 Because PD patients are vulnerable and burdened with frequent visits to multiple caregivers (e.g., their
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49 270 neurologist, physiotherapist, and speech therapist), it is important to burden the participants as minimally as
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51 271 possible. Therefore, during the process of designing this study and collecting the data, a multidisciplinary
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53 272 approach was established between neurologists and dentists to enable an as efficient as possible usage of the
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55 273 patient’s time and energy.
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59 275 The targeted number of inclusions will be a challenge. However, the calculated sample size is an estimation,
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61 276 because no clinical prevalences are known as yet. Like in otherwise healthy individuals, clenching and grinding
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63 277 are not always recognized by the patients themselves^{68,69}, thus the prevalence of sleep bruxism in the pilot
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65 278 study could have been underestimated. This means that the calculated sample size in this study might be
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67 279 higher than eventually required. Therefore, an interim analysis will be performed after 130 included
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69 280 participants or 6 months.
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73 282 This study has no longitudinal character and therefore, no causal relations can be observed between the (in-)
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75 283 dependent variables. Also, polysomnography is the golden standard to detect sleep bruxism while in the
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77 284 present study, a portable electromyographic recorder will be used⁶¹. However, since this device will be used

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3 285 for several nights in a row, the fluctuating character of sleep bruxism can be taken into account and is
4 286 therefore considered a good proxy for definite sleep bruxism⁵⁹. It should be noted, however, that the portable
5 287 recorder will fail to enable a distinction between jaw-muscle activities related to sleep bruxism and those
6 288 related to other orofacial movement disorders like oral dyskinesia and oro-mandibular dystonia⁷⁰. This is an
7 289 important issue, because such movement disorders can be present in patients with PD related to their
8 290 medication usage. In fact, in their updated international consensus paper on bruxism, Lobbezoo et al. (2018)
9 291 added the phrase that bruxism is a masticatory muscle activity in “otherwise healthy individuals”⁶¹. People
10 292 living with PD are certainly not “otherwise healthy”. In the later stages of levodopa-treated PD, dyskinesias,
11 293 including oral dyskinesias, commonly occur⁷⁰. Hence, the question could be raised if the masticatory muscle
12 294 activity observed in people with PD is “bruxism” at all. This calls for caution in the interpretation of the
13 295 bruxism-related findings of this study. Fortunately, in the questionnaire and clinical examination of the MDS-
14 296 UPDRS³⁹ (Table 2), the presence of oral dyskinesia and oro-mandibular dystonia is included. Hence, it is
15 297 possible to correct for their presence in the data analysis.

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17 299 This study does not include a control group. This limits the interpretation of whether the prevalence of
18 300 bruxism or TMDs is low or high in people with PD, which will only be possible by comparing the findings with
19 301 prevalences as reported in the literature. In addition, since tooth wear in older people reflects a lifetime of
20 302 factors, it will be also difficult to interpret the tooth wear findings in people with PD without having the
21 303 possibility for a direct comparison with similar individuals without PD. Also in this case, comparisons should be
22 304 sought with literature data. These issues should be considered limitations of this study.

23 305

24 306 In conclusion, this study will give more detailed information about the presence of bruxism and TMD pain in
25 307 patients with PD, as well as about possible associated factors like medication usage and severity of the disease.
26 308 Finally, more clinically relevant information will become available for dentists and other oral health care
27 309 professionals about the amount of tooth wear and the composition of saliva in patients with PD.

30 310 **Ethics and dissemination:**

31 311 This study protocol has been approved by the Medical Ethics Review Committee of Amsterdam UMC, location
32 312 VUmc; NL. 2019.143). Informed consent will be obtained from all participants. A data monitor will meet
33 313 annually to primarily concentrate on the safety of patients, and will be monitoring the collected data and
34 314 informed consents. The results will be published in peer-reviewed journals, if relevant presented at
35 315 conferences, and published as part of a Ph.D. thesis.

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37 317 Due to the sensitive nature of personal information, all data will be blinded and stored in secure
38 318 environments. Only the executive researcher and the head of the department can reach the unblinded
39 319 informed consents and the key for unblinding. These are stored separately. Digital data will be stored
40 320 pseudonymized in a secure database using Castor EDC (CDISC, Amsterdam, Netherlands). Detailed methods for
41 321 data management and storage can be obtained by contacting the corresponding author.

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3 322 **Authors contribution**
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5 323 All authors (MV, MK, KvD, HB and FL) were involved in designing this study. MV obtained the approval of the
6 324 Medical Ethics Review Committee and drafted the manuscript. Finally, all authors (MV, MK, KvD, HB and FL)
7
8 325 gave feedback on the draft and approved the final manuscript.
9

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11
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19 331 **Competing interest**

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22
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30 Figure Legends

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34 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 PD 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.
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48 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).
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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.

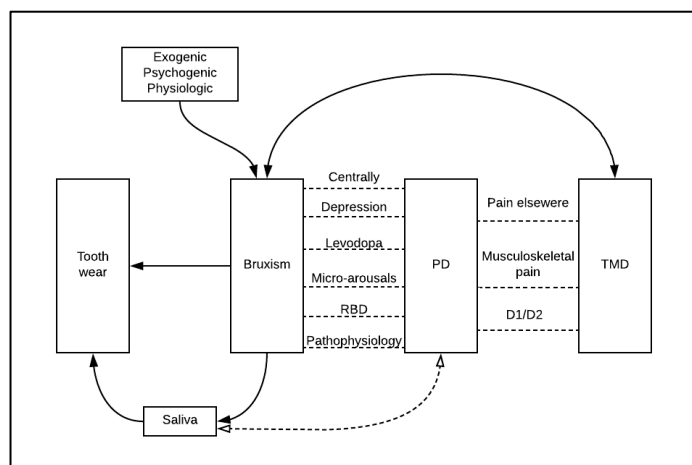


Figure 1. Visualization of the possible interactions between the different research variables. *Parkinson's Disease (PD)* is associated with bruxism through different variables: the dopaminergic system (pathophysiology) plays a role in both conditions; the prodromal phase of PD (RBD) shows the same characteristics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

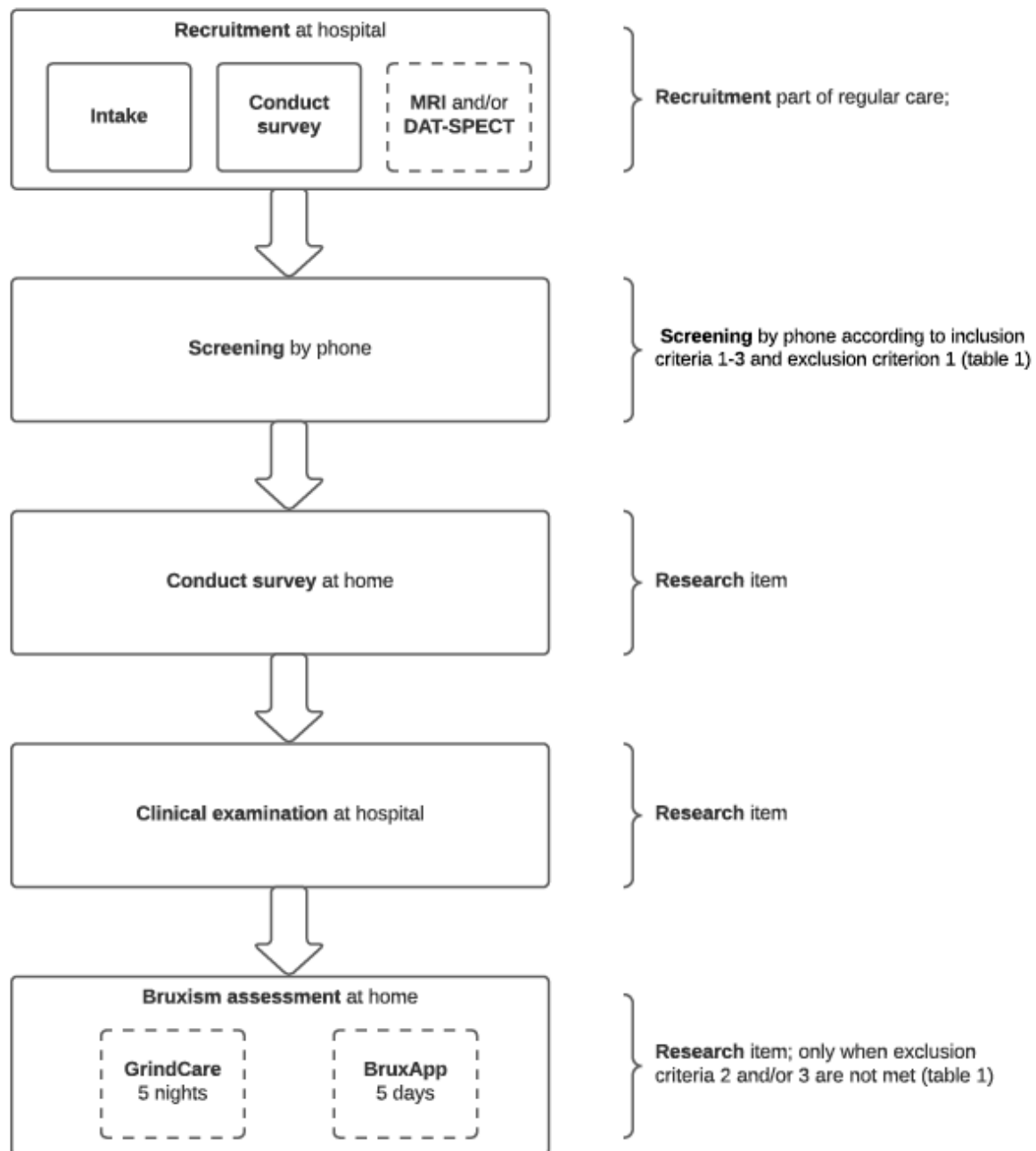


Figure 2. Flowchart of the study in which a distinction was made between the attendance of participants at the hospital and the study components at the participant's home. The intake and first survey is part of the regular care at the hospital, and only followed by an additional MRI and/or DAT-SPECT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

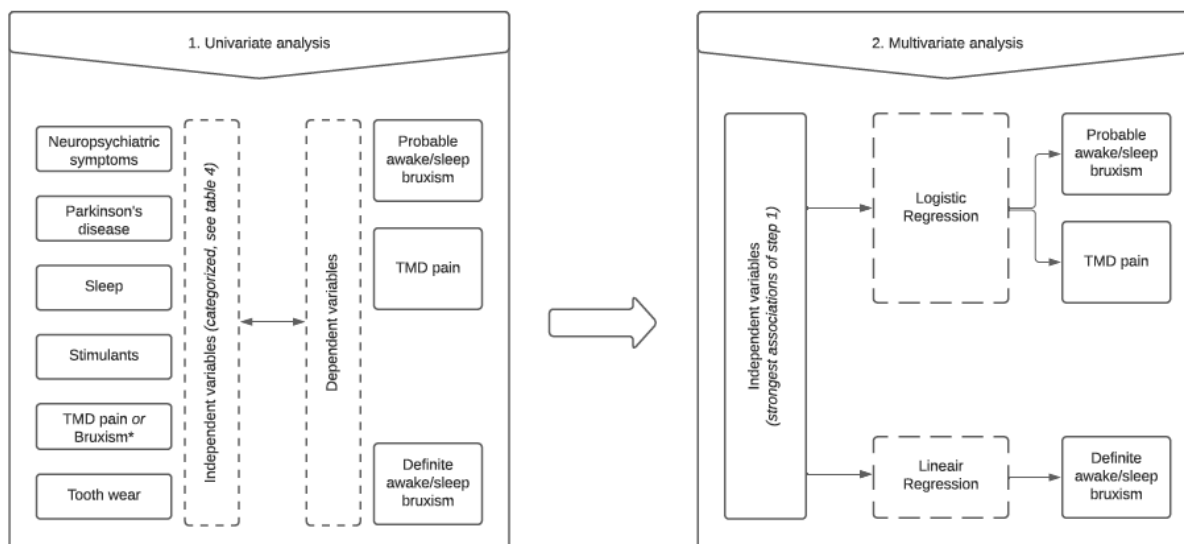


Figure 3. Flowchart of the data-analysis related to the first secondary aim: “to investigate which factors are influencing the presence of probable awake/sleep bruxism, TMD pain and the frequency of definite awake/sleep bruxism”. All variables will be tested individually to see whether an association 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 stage¹.
- 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 \leq 32)”, “moderate (score 33-58)”, and “severe (score \geq 59)” motor problems⁵.

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 \geq 11 on that subscale)”, “episodic anxiety (score \geq 6 on that subscale)”, “avoidance behavior (score \geq 5 on that subscale)”, and “any anxiety disorder score (score \geq 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-NL¹⁷ 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 screened²⁰. 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 were 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 $\leq 1/3$ (score 2)”, “loss of crown height $>1/3$ but $<2/3$ (score 3)” and “loss of crown height $\geq 2/3$ (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

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3 with scores 0 till 2: “not at all (score 0)”, “several days (score 1)”, and “more than half of the days/nearly
4 every day (score 2)”. Scores of 0, 5, and 15 are the cut-off points for “low”, “median”, and “high somatic
5 symptom severity”, respectively.
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10 11 Appendix 2

12 The following formula was used for the sample size calculation:

$$13 n = (Z^2P(1-P))/d^2$$

14 Z = Z statistic for a level of confidence

15 P = expected prevalence or proportion (in proportion of one)

16 d = precision

17 For the level of confidence of 95%, Z value is 1.96.

18 With an assumed prevalence of 46% (WB according pilot study), P is 0.46

19 With a precision of +/-5 percentage points (0.05), d should be set at 0.05.
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22 The numbers for the secondary aims are obtained when reaching the sample size for the primary aim. The
23 approach for the sample size calculation of the secondary aims are as follows:

24 Since no clinical data of the variables that will be studied are available yet in a population with PD, an effect
25 size is not known for our outcome measures. Nevertheless, in a recent questionnaire-based study, an
26 association between PD on the one hand and bruxism and TMD pain on the other was reported²⁶. The
27 prevalence found for these outcome measures were 46.0%, 24.3%, and 29.5% for awake bruxism, sleep
28 bruxism, and TMD pain, respectively. In the current study, a total of 6 independent categorized variables (see
29 Table 4) will be analysed to determine if they are associated with the presence of probable and definite
30 bruxism and/or TMD pain in patients with PD, by means of logistic and linear regression analyses (see statistical
31 approach). We assume that only four predictors will be eligible for multivariate analysis, because (i) only
32 predictors with the strongest associations are included, and (ii) predictors will drop out due to their probable
33 association with each other. The literature about numbers of observations in participants per variable (events)
34 in a logistic regression analysis indicated that for each predictor in a regression analysis, data from 10-20 events
35 is needed²⁷. Consequently, 15 events are chosen and thus (4x15=) 60 events are needed. Based on the
36 prevalence of the recent questionnaire-based pilot study²⁶, 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 needed²⁶. For the linear regression, this estimate of the sample size is sufficient to detect medium and large effect sizes²⁸. 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.
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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	1. Hypersalivation	1. >7.5	1. Abnormal	1. 10-12	1. Normal/high
	2. 0.50-0.25	2. Normal	2. 7.5-6.8	2. Normal	2. 6-9	2. Low
	3. 0.24-0.10	3. Risk	3. 6.7-6.5	3. Risk	3. 0.5	3. Very low
	4. <0.10	4. Pathologic	4. <6.5	4. Pathologic		
During chewing	1. >2.00	1. Hypersalivation	1. >8.0	1. Abnormal	1. 10-12	1. Normal/high
	2. 2.00-0.75	2. Normal	2. 8.0-7.0	2. Normal	2. 6-9	2. Low
	3. 0.74-0.50	3. Risk	3. 6.9-6.5	3. Risk	3. 0-5	3. Very low
	4. <0.50	4. Pathologic	4. <6.5	4. Pathologic		

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