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Technology-based assessment of motor and non-motor phenomena in Parkinson disease

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ABSTRACT

Introduction: The increasing development and availability of portable and wearable technologies is rapidly expanding the field of technology-based objective measures (TOMs) in neurological disorders, including Parkinson disease (PD). Substantial challenges remain in the recognition of disease phenomena relevant to patients and clinicians, as well as in the identification of the most appropriate devices to carry out these measurements.

Areas Covered: The authors systematically reviewed PubMed for studies employing technology as outcome measures in the assessment of PD-associated motor and non-motor abnormalities.

Expert Commentary: TOMs minimize intra- and inter-rater variability in clinical assessments of motor and non-motor phenomena in PD, improving the accuracy of clinical endpoints. Critical unmet needs for the integration of TOMs into clinical and research practice are the identification and validation of relevant endpoints for individual patients, the capture of motor and non-motor activities from an ecologically-valid environment, the integration of various sensor data into an open-access, common-language platforms, and the definition of a regulatory pathway for approval of TOMs. The current lack of multi-domain, multi-sensor, smart technologies to measure in real time a wide scope of relevant changes remain a significant limitation for the integration of technology into the assessment of PD motor and non-motor functional disability.

Key words: biomarker, Parkinson, technology, motor symptoms, non-symptoms, trial

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1. INTRODUCTION

5 Parkinson disease (PD) is a multisystem neurodegenerative disorder resulting in a complex
6 pattern of disability due to the impairment of both motor (i.e., tremor, bradykinesia, rigidity) and
7 non-motor (i.e., cognition, sleep, autonomic) functional systems [1]. PD-associated clinical
8 features are usually quantified by clinicians using validated clinical scales, such as the
9 Movement Disorder Society Unified Parkinson’s disease Rating Scale (MDS-UPDRS) [2], and
10 the Non-Motor Symptoms Scale for Parkinson’s disease (NMSS) [3]. These instruments,
11 however, are prone to limitations such as subjectivity, inter-rater variability, and limited
12 accuracy in capturing small variations between and within patients.
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20 Technology advancements have expanded the application of a new generation of technology-
21 based objective measures (TOMs) to detect and monitor a functional range critical for the
22 comprehensive characterization and long-term monitoring of patients with PD [4,5]. TOMs may
23 capture multiple motor activities, such as frequency and amplitude of movements, severity of
24 tremor and dyskinesia, and extent of gait and postural impairment [6–8]. In addition, TOMs may
25 characterize non-motor phenomena that cannot be captured by conventional clinical scales, such
26 as sleep architecture, respiratory rate, beat-to-beat blood pressure changes, heart rhythm
27 variability (HRV), and electroencephalographic (EEG) activity [9,10].
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36 By reducing the standard deviation of clinical endpoints and minimizing intra- and inter-rater
37 variability in clinical assessments, TOMs have the potential to improve the quality of diagnostic
38 definitions [11]. Multiple challenges, however, limit the integration of TOMs into the clinical
39 and research practice, including standardization of extracted parameters, cost of technology,
40 patient compliance [12], and risk of producing outcome measures that have little practical
41 meaning to end-users [13,14]. In order to be purposeful, any measures of function need to
42 represent variables that are important to patients and can be amenable to interventions by
43 clinicians and researchers [15].
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51 We sought to systematically review studies that employed technology for the evaluation of motor
52 and non-motor phenomena in PD, appraising the extent of current integration of TOMs into the
53 assessment of functional disability.
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2.1 BODY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16].

2.1.1 Search Methods

We searched PubMed for human studies published in English between January 1980 and June 2018 using a combination of free text and MeSH (Medical Subject Headings) for the following terms (Table e-1, online): Parkinson, smartphone, sensor, palm, computer, accelerometer, tablet, digital, electronic, microphone, gyroscope, actigraphy, gait analysis, voice analysis, pedometer, smartwatch, barometer, wearables, applications, apps, Wi-Fi, internet, Bluetooth, battery, touchscreen, camera, oximeter, facial recognition, tilt table, CANTAB, electroencephalogram, electrocardiogram, electromyogram, electronic diary, UPSIT. No restrictions were applied to gender, age, ethnicity, disease duration, or disease severity.

2.1.2 Inclusion and Exclusion Criteria

We included original studies employing TOMs as primary, secondary, or exploratory outcomes for the qualitative or quantitative assessment of symptoms, severity, and functional disability associated with PD. We excluded case reports, review articles, and studies using imaging, genetic, or corporal fluids (e.g., blood, cerebrospinal fluid) sampling technologies.

2.1.3 Selection of studies

Abstracts were independently reviewed for eligibility criteria by 2 investigators (A.S. and S.S.). Disagreements were anticipated to be settled by consensus among the authors. Duplicated studies were identified and excluded. The reference lists of selected articles were additionally screened for pertinent studies not included in the original search strategy.

2.1.4 Data Extraction and Assessment of risk of bias

The following data were extracted from eligible studies using a standardized form: a) year of publication; b) study design; c) study population; d) inclusion and exclusion criteria; e) primary and secondary outcome measures; f) results; and g) study limitations. Given the heterogeneity of study designs, we followed the Cochrane handbook recommendations and assessed the risk of

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3 bias of individual studies utilizing the National Heart, Lung, and Blood Institute tools (NHLBI)
4 [17], as per the Cochrane handbook recommendations [18]. These tools are tailored to study
5 types (i.e., cross-sectional, case-control, interventional) and include a qualitative, internal
6 validity checklist (“Yes”, “No”, and “Non-applicable”) for domains such as methodological
7 pertinence, potential sources of bias, confounding, and adequacy of results for quality
8 classification as "good," "fair," or "poor". In general, a "good" rating applies to studies with low
9 risk of bias whose results are deemed valid; "fair" to studies susceptible to some biases but
10 deemed insufficient to invalidate their results; and "poor" to studies with significant risk of bias.

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19 **2.1.5 Data Analysis**

20 Included studies were categorized per functional domain investigated (motor vs. non-motor) and
21 sorted per year of publication and technology employed. Results were summarized in tables and
22 discussed in the text.
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28 **2.2 Results**

29 The search strategy resulted in the identification of 2941 studies published between 1980 and
30 2018. A total of 2817 studies did not meet all inclusion criteria or were considered duplicates
31 (Figure 1). Thus, we included 124 studies (106 cross-sectional, 11 case-control, and 7
32 prospective cohorts) which underwent data extraction and individual appraisal of the quality of
33 evidence and risk of bias (Table e-2 and e-3, online).
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39 There were 61 studies (59 cross-sectional and 2 case-control) employing TOMs for the
40 assessment of qualitative measures of motor phenomena such as gait and postural instability (n=
41 33 studies), bradykinesia (n= 13 studies), tremor (n= 8 studies), and rigidity (n= 7 studies), and
42 63 studies (48 cross-sectional, 7 prospective cohort, and 8 case control) employing TOMs for the
43 assessment of non-motor phenomena such as sleep disorders (n= 23 studies), cognitive
44 impairment (n= 18 studies), dysautonomia (n= 12 studies), visual deficits (n= 3 studies), and
45 voice analysis (n= 7 studies) (Figure 2). The overall number of published studies integrating
46 TOMs into the assessment of PD-associated motor (gait, postural stability, bradykinesia, rigidity,
47 tremor) and non-motor (sleep, cognitive function, autonomic function, speech) deficits have
48 steadily increased over the years (Figure 3).
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2.2.1 Gait and Posture Stability

Kinematic systems [19–43] and wearable sensors [44–50] were employed in the assessment of temporal (reaction time, gait cycle duration), spatial (step length, step height) and biomechanical (ankle torque, vertical landing force) variables of gait, and in the evaluation of gait strategies (i.e. number of steps, single versus multiple step response) during treadmill-based assessments or instrumented walking tests, such as the timed-up-and-go [29,38,44,46]. Balance and postural instability were assessed using force platforms [27,28,32,37,51–55] and wearable sensors [44–48] (Figure 3) to measure the trajectory of the center of pressure (COP) and center of mass (COM) misplacement [22,23,28,32,53], as well as the trunk acceleration [53] during backwards pull [27,32,48,52], double task tests [51], and postural sway with eyes open and eyes closed [23]. Significant differences were observed in PD patients versus healthy controls in spatial and temporal gait variables [30,32,40,47,55], as well as in the postural response to external perturbations [32]. Gait parameters were also used to assess the progression of PD-associated gait and postural instability [22,24,25,27,28,37,45,47,52,53] and to assess the response to pharmacological [29] and non-pharmacological [20] therapies (Table 1).

Kinematic and EMG measurements were employed to assess turning and freezing of gait (FOG), evaluating both spatial and temporal gait parameters [30,50,56], as well as the pattern of axial muscle activation during turns [33]. Freezers showed greater variability in stride length, stride time, and cadence compared to non-freezers [30,50,56] along with reduced thoracic adaptation to hip movements during gait and turns [31,33,34], increased number of steps, prolonged turning time [57], and decreased range of motion in the ankle and hip joints immediately before FOG episodes [35].

2.2.2 Bradykinesia and Rigidity

Wearable sensors [58–60], infrared cameras [19,21,26,61,62], tablet-based measurements [63,64], Diadochokinesimeter [65], dexterity pegboard [66], and light emitting diode (LED) photosensitive system [67] were used to evaluate amplitude, smoothness, and peak velocity of movements during standardized motor tasks such as finger tapping [21,61,63], pronation-supination [65], reach-to-grasp [19,26,62], wrist extension [59], goal directed movements [60],

handwriting [64], and facial expression [67–69]. Muscle rigidity was evaluated using a dynamometer [54,70].

There were similar reaction times and movement lengths in PD patients vs. healthy controls, but lower maximum speed and, consequently, longer execution time in PD [19,39]. TOMs accurately captured changes in transport time, wrist velocity, and arm acceleration during reach-to-grasp motor tasks [26,62]. Tablet-based measurements objectively quantified amplitude, velocity [64], and motor blocks during handwriting [63]. Wearable sensors were used to assess the effect of dopaminergic medications on speed and amplitude of movements, showing a more pronounced effect on the former [71]. Finally, optokinetic analyses were employed to assess orofacial movements, such as vertical jaw movements during speech [67] and hypomimia [68,69], showing sufficient accuracy in objectively capturing differences between PD patients and healthy controls (Table 2).

A study evaluated PD-associated trunk rigidity using a dynamometer to measure resistive torques during passive trunk flexion and extension [54]. The internal validity of this approach was confirmed by different authors reporting a direct correlation between dynamometer-based rigidity assessment and health-related quality of life in PD [70]. Unlike this study, however, most studies did not evaluate the extent to which changes measured by specific TOMs correlated with relevant changes as perceived by patients.

2.2.3 Tremor

Accelerometer- [72–75], gyroscope- [76,77], EMG- (72–74,78), kinematic- [72], and tablet-based [79] measurements were used to capture key phenomenological characteristics of tremor, namely frequency, amplitude, and variability under different testing conditions. TOMs effectively differentiated between parkinsonian, essential [76,77,79], and functional (psychogenic) tremors [78], and provided objective measurements of tremor severity in real-life condition using both wearable devices [74] and smartphone applications [75,80].

TOMs were also employed in the detection of subclinical tremor [73] and the analysis of the different tremor components during resting, movement initiation, and decelerating phase of movement [72]. Innovative machine-learning algorithms have been recently developed to

evaluate the variability of tremor in the time-domain during resting and motor activities [76,77] (Table 2).

2.2.4 Speech

Multi-dimensional voice software programs for acoustic analysis (i.e., Praat, a freeware developed by the University of Amsterdam) have been employed for the quantitative assessment of amplitude, prosody, speed, grammar, and fluency of speech during sustained-vowels phonation, alternating and sequential motion rates, and normal reading [81]. TOMs proved useful in sensitively capturing differences in speech between PD patients and healthy controls, including maximal phonation time, phonation quotient, percent jitter, percent shimmer, and noise-to-harmonic ratio [81–83], suggesting their employment in the diagnostic assessment of PD [84], monitoring of PD-associated functional disability [85], and prognostic assessment of functionally relevant outcomes such as cognitive decline [86]. An automated speech assessment has been proposed as part of a battery of test, including also posture analysis, gait assessment, finger tapping, and response time, to monitor PD symptoms at the home environment using commercially available smartphone applications [87] (Table 3).

2.2.5 Sleep

Sleep studies employed polysomnography (PSG) and actigraphy to evaluate the quality of sleep in PD [88–92], or to diagnose PD-associated conditions such as sleep apnea [92,93], REM sleep behavior disorders [92–99], sleep attacks [100–102], periodic limb movements [103], and nocturia [104]. The effect of pharmacological and non-pharmacological treatments on nocturnal sleep quality was also investigated using PSG [100,105–107].

Fragmented sleep architecture and reduced quality of sleep were found both in mild and advanced PD [108], with strong correlation between sleep efficiency, as measured by the PSG, and clinical measures of sleep quality, such as the Epworth sleepiness scale (EPSS), the PD sleep scale (PDSS), and the Pittsburgh Sleep Quality Index (PSQI) [109]. Additional studies evaluated the effect of pharmacological and non-pharmacological treatments on PD-associated quality of sleep, reporting an objective improvement in the architecture of sleep with advanced therapeutic

options such as levodopa/carbidopa intestinal gel infusion (LCIG) [106] and subthalamic nucleus deep brain stimulation [107]. (Table 4).

2.2.6 Cognitive Function

Electroencephalographic (EEG) spectral analysis was used to evaluate cognitive function in PD [110–114], demonstrating a correlation between slow EEG rhythm in the temporo-occipital regions and poor performance on visuospatial tests [113,115], as well as a correlation between increased risk of dementia and slow EEG activity in the posterior regions during REM sleep, and in the temporal regions during wakefulness [112,115–118]. Promising yet preliminary results were reported by studies investigating the application of evoked potential-based measures in the differential diagnosis of PD [119,120] and in the assessment of PD-associated cognitive dysfunction [116–118,121–127], visual impairment [127–129], and behavioral disorders [130] (Table 3).

2.2.7 Autonomic Function

Cardiovascular and sweating autonomic testing, as well as HRV and 24-hour ambulatory blood pressure monitoring have been employed in the assessment of sympathetic [131,132] parasympathetic [132,133], and cholinergic autonomic function [10]. Significant differences were observed between PD and healthy controls suggesting a role for autonomic testing in the diagnostic classification of PD [134], characterization of patients at risk of poor functional outcome [135] or higher risk of dementia [136], and in distinguishing PD from atypical parkinsonian syndromes [137,138]. Recent studies also suggested that failure at the autonomic function testing might predict disease progression and survival in PD [139], as well as assist in the identification of patients expected to respond differentially to a range of treatments [140] (Table 5).

3. CONCLUSION

This systematic review showed that an increasing number of studies employed TOMs for the assessment of PD-associated motor and non-motor phenomena over the last two decades (Figure 5). A range of technologies were used to evaluate motor endpoints such as gait, balance, bradykinesia, tremor, rigidity, and speech, as well as non-motor endpoints such as sleep,

cognition, and autonomic function. TOMs demonstrated the potential of capturing motor and non-motor phenomena with greater accuracy and reduced intra- and inter-rater variability than clinical scales and self-administered questionnaires. However, only a few studies correlated TOMs with patient-centered clinical scales, quality of life questionnaires, or handicap index. In addition, minimal clinically important differences have been estimated for a limited number of TOMs.

A possible limitation of our study consists of a searching strategy limited to published studies. We did not conduct searches in multiple databases, as well as Grey Literature or ongoing trials (e.g., clinicaltrials.gov). Thus, our conclusions do not take into consideration currently ongoing research endeavors.

4. EXPERT COMMENTARY

While substantially improving the accuracy of both motor and non-motor clinical endpoints in PD, ultimately resulting in improved diagnostics and monitoring of functional disability [11], the integration of TOMs into randomized controlled trials and routine clinical practice remains limited by several unresolved issues [141]. An important roadblock is the lack of a clear regulatory pathway from the FDA and the EMA for the routine employment of TOMs in both clinical and research settings. Less than 3% of ongoing clinical trials of neurodegenerative disorders have employed TOMs as an outcome measure. However, a survey from medical directors from pharmaceutical companies indicated that the majority of them are considering using TOMs in future clinical trials within the next five years [141]. Also, a smartwatch for the monitoring of epileptic seizures was recently approved by regulatory agencies based on data demonstrating their accuracy and usefulness in clinical practice [142,143]. This preliminary experience encourages similar studies in the field of movement disorders.

The ideal outcome measure would be objective, exhibit minimal intra- and inter-operator variability, continuously capture relevant data in the patient's home environment, and sensitively capture small but meaningful changes over a prolonged period of time. Available TOMs meet some of these criteria but fail others, such as capturing motor and non-motor activities from an ecologically-valid environment. Currently, most of the gait and balance measures rely on tests

assessing the patient’s functional capacity (e.g., timed-up-and-go) rather than functional activity (e.g., continuous recording of natural unrestricted gait). In addition, the resolution of biomechanical sensors remains restricted to the anatomical area on which the sensors are applied, possibly yielding low quantitative agreement with the broader range of motor disability, quality of life, and other measurable patient-relevant endpoints [11,144].

The assessment of non-motor symptoms poses even more significant challenges due to the frequent use of cumbersome technologies such as PSG, EEG, or tilt table, which highlight the need for a tradeoff between the comprehensiveness of the assessment and their ecological validity. Simplified sleep measurements collected from an actigraphy may be preferred over the more accurate but less ecologically representative PSG [145]. A similar context applies to the evaluation of autonomic function. In a recent publication [146], we proposed that a 24h-ambulatory blood pressure monitoring might be effectively employed as a screening test for cardiovascular autonomic neuropathy, a disabling comorbidity in PD with relevant socio-economic impact [147]. Autonomic dysfunction remains under-recognized and under-treated in PD [148] in part because its ascertainment relies on cardiovascular autonomic testing available only in a few specialized laboratories. In conclusion, these findings highlight the urgent need for developing relatively simple and unobtrusive systems to monitor motor and non-motor endpoints in the home and community settings rather than during in-hospital evaluations.

A significant limitation consists of the lack of a multi-sensor, open-access, common-language platform combining the results of different sensors into a multi-dimensional TOM expressing a global measure of PD-associated functional disability. Although this unmet need has been reiterated by the Movement Disorders Society (MDS) in various international meetings and position papers [149], diagnostic and monitoring systems developed by different manufacturers continue to remain incompatible with one another. As a result, it is difficult or impossible to combine data gathered by different TOMs. This point represents one of the most critical areas of need, identified by the MDS Task Force for the Integration of Technology in PD as requiring further development. Only few studies have employed a smartphone application that integrates the capture of voice, posture, gait, finger tapping, and response time in the patient home

environment, with high patient participation as well as sensitivity and specificity in the collected outcome measures [87].

5. FIVE-YEAR VIEW

Continuous improvements in technology are creating increasing opportunities for TOMs to improve self-management options and overall healthcare outcomes in PD. Thus, their integration into research and practice is expected to grow in the next five years. Critical challenges consist of validation of measures with patient-centered relevant endpoints, standardization of procedures, and approval by regulatory authorities.

KEY ISSUES

- Clinical scales for the assessment of Parkinson disease (PD) symptoms are prone to limitations such as subjectivity, inter-rater variability, and limited accuracy in capturing small variations within and between patients. A new generation of technology-based objective measures (TOMs) may provide a more accurate characterization of motor and non-motor phenomena associated with PD.
- We searched PubMed for human studies employing TOMs as primary, secondary, or exploratory outcomes for the qualitative or quantitative evaluation of PD-associated motor and non-motor symptoms. There were 61 studies assessing motor phenomena such as gait and postural instability (n= 33 studies), bradykinesia (n= 13 studies), tremor (n= 8 studies), and rigidity (n= 7 studies), and 63 studies assessing non-motor phenomena such as sleep disorders (n= 23 studies), cognitive impairment (n= 18 studies), dysautonomia (n= 12 studies), sensory deficits (n= 3 studies), and voice analysis (n= 7 studies).
- Although TOMs have the potential to significantly improve the accuracy of both motor and non-motor clinical endpoints, their integration into randomized controlled trials and routine clinical practice remains limited by several unresolved issues, including validation of patient-centered outcomes, standardization of measurements, and approval by regulatory authorities.
- While TOMs have not yet been shown to be superior to the clinical evaluation, their integration into research and practice is expected to substantially increase in the next five years and translate into enhanced care, better self-management options for PD patients,

and overall improved healthcare outcomes. A survey from 12 medical directors from pharmaceutical companies indicated that 83% of them are considering using TOMs in future clinical trials within the next five years.

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*** of considerable interest*

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FIGURES TITLES AND LEGENDS

Figure 1. Study selection algorithm

Out of 2941 records initially identified from our searching strategy, we screened 145 articles that were evaluated for eligibility, which eventually led to the inclusion of 124 studies that underwent data extraction and analysis.

Figure 2. Technology employed in the assessment of motor and non-motor phenomena in Parkinson disease

A wide range of technologies has been employed in the assessment of motor and non-motor phenomena of Parkinson disease. In the figure are reported systems/devices used along with the number of associated studies.

Figure 3. Number of studies employing technology-based objective measures in the assessment of motor and non-motor phenomena in Parkinson disease

An increasing number of studies have employed technology-based objective measures for the assessment of motor and non-motor phenomena associated with Parkinson disease over the last three decades.

Figure 4. Kinematic and Posture Analysis

A: Infrared camera, computerized walkway for gait analysis, and wearable sensors worn of each extremity and on the chest can be used to sensitively capture aspects related to patient’s mobility in the three axes of space, including neck, arm, and hip movements.

B: Force plate and wearable sensors can be used to estimate postural stability, which can be represented as a line indicating the postural sway of the center of mass over a 30-second period of time. Irregular and wide oscillations of the center of mass are indicative of postural instability.

Figure 5. Telehealth application for wearable technologies

Wearables have the potential to capture multiple motor and non-motor phenomena associated with Parkinson disease and transmit data using wireless Internet and Bluetooth connections.

Study selection algorithm.

Out of 2941 records initially identified from our searching strategy, we screened 145 articles that were evaluated for eligibility, which eventually led to the inclusion of 124 studies that underwent data extraction and analysis.

122x124mm (300 x 300 DPI)

Technology employed in the assessment of motor and non-motor phenomena in Parkinson disease. A wide range of technologies has been employed in the assessment of motor and non-motor phenomena of Parkinson disease. In the figure are reported systems/devices used along with the number of associated studies.

125x124mm (300 x 300 DPI)

Number of studies employing technology-based objective measures in the assessment of motor and non-motor phenomena in Parkinson disease.
An increasing number of studies have employed technology-based objective measures for the assessment of motor and non-motor phenomena associated with Parkinson disease over the last three decades.

210x165mm (300 x 300 DPI)

Kinematic and Posture Analysis.

A: Infrared camera, computerized walkway for gait analysis, and wearable sensors worn of each extremity and on the chest can be used to sensitively capture aspects related to patient’s mobility in the three axes of space, including neck, arm, and hip movements.

B: Force plate and wearable sensors can be used to estimate postural stability, which can be represented as a line indicating the postural sway of the center of mass over a 30-second period of time. Irregular and wide oscillations of the center of mass are indicative of postural instability.

49x48mm (300 x 300 DPI)

Telehealth application for wearable technologies.

Wearables have the potential to capture multiple motor and non-motor phenomena associated with Parkinson disease and transmit data using wireless Internet and Bluetooth connections.

46x24mm (300 x 300 DPI)

Table 1: Eligible Studies Assessing Gait and Postural Stability

Study	Design	Population	Selection Criteria	Aim	Technology	Results	Quality
Schlachetzki 2017	Cross-sectional	190 PD 101 HC	Inc: PD, H&Y< 4 Exc: movement limitations for conditions other than PD	Measure gait characteristics in PD	Wearable sensor (accelerometer and gyroscope)	Gait parameters differed between HC and PD at moderate disease stage and/or higher levels of motor impairment	Good
Son 2017	Cross-sectional	20 PD 10 HC	Inc: PD, H&Y< 4 Exc: movement limitations	Investigate turning in PD with 3D analysis during timed up and go	Motion analysis	Step length and foot clearance height, and timed up and go test during turning phase may be helpful turning measures in across multiple PD severities	Good
Conradsson 2017	Cross-sectional	19 PD 17 HC	Inc: PD, age ≥60, MMSE ≥24, H&Y 2 - 3 Exc: movement limitations, visual impairment	Determine if dopaminergic medication improves preplanned and unplanned walking turns in PD	Kinematic analysis	Turning impairments remained even after dopaminergic medication	Good
Pham 2017	Cross-sectional	24 PD	Inc: PD, severe self-reported freezing Exc: dementia, depression	Assess a model for detection of FOG in PD	FOG detector with kinematic analysis	FOG events can be detected with a automated single sensor located at the ankle or hip	Good
Pasluosta, 2015	Cross-sectional	139 PD	Inc: PD with pull test score 0-2 Exc: N/R	Assess postural instability in PD	Wearable sensor Accelerometer	PD foot motion estimates postural instability	Good
Švehlík 2009	Cross-sectional	20 PD 20 HC	Inc: PD, PD meds, Exc: other medical conditions affecting gait; dementia	Evaluate time-distance, stride length, and ankle range of motion during gait in PD	Motion analysis Force plate	PD patients have slower and shorter stride length and reduced ankle range of motion	Good

Kim 2009	Cross-sectional	7 PD 14 HC	Inc: PD Exc: N/R	Evaluate postural responses of patients with PD during perturbation	Force plate Kinematic analysis	PD showed worse ankle feedback gain during perturbation	Good
Cho 2009	Cross-sectional	10 PD 7 HC	Inc: PD Exc: N/R	Examine walking dynamics in PD	Motion analysis	PD has greater gait impairment with decreased foot control and arm swing dynamics	Good
McVey 2009	Cross-sectional	10 PD 10 HC	Inc: PD Exc: N/R	Estimate postural instability in PD	Force plate Kinematic analysis	Early PD has greater postural instability vs. HC	Good
Alice 2007	Cross-sectional	10 PD	Inc: PD, history of FOG Exc: medical conditions affecting gait other than PD	Describe strides characteristics prior to freezing vs. voluntary and ongoing gait	Kinematic analysis	PD had decrease in ankle and hip joint range of motion prior to freezing, with preserved movement shape	Good
Hong 2007	Cross-sectional	12 PD 16 HC	Inc: PD, mild turning problems Exc: N/R	Determine if PD retain turning ability after rotating platform walking	Kinematic analysis	PD retained turning ability after rotating platform walking task	Good
Ferrarin 2005	Cross-sectional	10 PD	Inc: PD, bilateral STN DBS, severe motor fluctuations, response to L-dopa Exc: dementia, depression, abnormal cerebral MRI, other illnesses	Assess the effects of L-dopa and STN DBS separately and combined on gait in PD	Kinematic analysis	PD meds and bilateral STN DBS additively and synergistically improve gait parameters such as speed, stride length, and ROM of knee and ankle joints	Good
Stolze 2001	Cross-sectional	9 PD 10 HC	Inc: Bilateral STN stimulation Exc: N/R	Examine the impact of STN-DBS on gait in PD	Kinematic analysis	STN-DBS increases gait velocity and stride length	Good
Parisi 2015	Cross-sectional	34 PD	Inc: N/R Exc: N/R	Correlate wearable sensor data with UPDRS	Wearable sensor	Wearable sensor accurately predicted UPDRS scores	Fair

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Chomiak 2015	Case-control	24 PD w&w/o freezing	Inc: PD, walking unassisted Exc: dementia, diseases that affect gait	Evaluate if stepping-in- place with a concurrent mental task can be used for evaluating cognitive–motor deficits in PD	Kinematic analysis	Step height was significantly worse in PD during concurrent subtraction and stepping-in-place tasking	Fair
Dillmann 2014	Cross- sectional	40 PD 25 HC	Inc: akinetic-rigid PD Exc: resting or postural tremor	Analyze movements of the upper and lower limbs in PD	Kinematic analysis Treadmill- based assessment	PD demonstrated greater intersegmental coordination	Fair
Barbe 2014	Case-control	34 PD w&w/o freezing	Inc: PD, akinetic-rigid, right handed, age 40 – 80 Exc: depression, dementia, movement limitations	Assess spatial and temporal gait variability between FOG episodes in freezers vs. non- freezers	Kinematic analysis	Freezers have a higher spatial gait variability between freezing episodes	Fair
Moore 2013	Cross- sectional	25 PD	Inc: PD, self-reported freezing, MMSE $\geq$ 24 Exc: dementia, major depression	Evaluate sensor placement for accuracy in detecting FOG in PD	Kinematic analysis Acceleromete r	A simpler single lumbar sensor had comparable accuracy to a 7 sensor system for detecting FOG	Fair
Zampieri 2011	Cross- sectional	6 PD 8 HC	Inc: N/R Exc: no space in home to walk 5-7 meters	Evaluate stride length, stride velocity, cadence, peak arm swing velocity, and turning velocity during Timed Up and Go	Wearable sensor	PD exhibited faster gait in laboratory than at home, although with shorter gait and steps in both conditions vs. HC	Fair
Merello 2010	Cross- sectional	20 PD 17 HC	Inc: PD Normal MRI H&Y in OFF = 3 Exc: dementia	Evaluate COM, COP, step length, and speed changes during festination in PD	Kinematic analysis	Patients with festination attempt to align COP to COM	Fair
Salarian 2010	Cross- sectional	12 PD 12 HC	Inc: H&Y 1 to 2.5, no history of PD drugs Exc: other neurological disorders, orthopedic disorders/devices	Evaluate cadence, turning duration, and arm-swing angular velocity during Time Up and Go	Wearable sensor	PD demonstrated slower cadence and arm swing angular velocity and longer turning time duration	Fair

Ganesan 2010	Cross-sectional	20 PD 20 HC	Inc: H&Y = 2, stable PD meds, normal pull test, right dominance Exc: cognitive deficits, depression, motor fluctuations, orthopedic problems	Evaluate subclinical balance impairment in PD with normal pull test	Force plate	PD patients had subclinical direction-specific balance impairment	Fair
Johnsen 2010	Cross-sectional	22 PD	Inc: PD, STN DBS Exc: inability to walk	Evaluate the effect of anatomical position of STN DBS on gait in PD	Kinematic analysis	Step velocity, step length, and balance had greater improvement with dorsal STN DBS compared to ventral STN DBS in PD.	Fair
Cantinioux 2010	Cross-sectional	11 PD 11 HC	Inc: PD, bilateral STN DBS Exc: other walking or speech disorders	Assess the effects of L-dopa and STN DBS on gait and speech patterns in PD vs. HC	Kinematic analysis Speech analysis	Walking and speech velocity were correlated, but STN DBS and L-dopa improved walking velocity while having no effect on speech velocity	Fair
Mancini 2009	Cross-sectional	11 PD 12 HC	Inc: PD, no history of PD meds Exc: other neurologic disorders or gait impairments	Evaluate anticipatory postural adjustments and characterize step initiation deficits in PD	Force plate Accelerometer	Untreated PD exhibited smaller peak trunk acceleration vs. HC	Fair
Hong 2009	Cross-sectional	11 PD 12 HC	Inc: PD Exc: N/R	Determine objective differences in turning in PD vs. HC during a turning task	Kinematic analysis EMG	PD differed from HC in axial control but had similar lower limb muscle patterns during turning task	Fair
Stack 2008	Cross-sectional	28 PD 12 HC	Inc: PD, walk w/o assistance Exc: Neurological comorbidities	Analyze differences in turning in PD vs. HC during a turning task	Motion analysis	PD differed on step count, time, and quality of turn versus HC	Fair
Huxham 2008	Cross-sectional	10 PD 10 HC	Inc: PD Exc: N/R	Analyze head and trunk rotation of PD vs. HC during walking turns	Kinematic analysis	PD demonstrated greater rotation of head and trunk versus HC	Fair
Carpinella 2007	Cross-sectional	6 PD	Inc: PD, UPDRS part III score 12 – 20 Exc: N/R	Quantitatively describe locomotor symptoms in mild PD	Kinematic analysis Force plate	Early stage of PD had mild alterations of steady-state linear walking and in transitional conditions during direction changes	Fair

Ferrarin 2002	Cross-sectional	4 PD 4 HC	Inc: PD, STN DBS Exc: N/R	Assess gait changes with STN DBS in PD vs. HC	Kinematic analysis Force plate	STN DBS improves gait patterns in PD but reduces ankle power production during stimulation	Fair
Van Emmerik 1999	Cross-sectional	27 PD 11 HC	Inc: recent PD diagnosis Exc: PD meds	Evaluate coordination and stability during walking in PD	Kinematic analysis	Analysis of changes in velocity during walking can identify coordination deficits and trunk rigidity.	Fair
Doan 2010	Cross-sectional	10 PD 8 HC	Inc: PD Exc: N/R	Evaluate standing and reaching in a challenging environmental context	Force plate	PD delayed trunk flexion and peak end-point velocity	Poor
Bleuse 2008	Cross-sectional	10 PD 10 HC	Inc: PD Exc: N/R	Describe postural instability in PD vs. HC during limb movement	Force plate	PD had postural instability prior to limb movement	Poor

PD, Parkinson’s disease; HC, Healthy control; Inc, Inclusion; Exc, Exclusion; w&w/o, with and without; N/R, non-reported; min, minutes; REM, Rapid eye movement; DBS, Deep brain stimulation; STN, Subthalamic nucleus; COM, center of mass; COP, center of pressure; H&Y, Hoehn & Yahr; MMSE, Mini-Mental State Examination; ROM, range of motion

Table 2: Eligible Studies Assessing Bradykinesia, Rigidity, and Tremor

Study	Design	Population	Selection Criteria	Aim	Technology	Results	Quality
Rabelo 2017	Cross-sectional	15 PD 12 HC	Inc: Older patients with PD Exc: Dementia, upper limb movement limitations	Propose and evaluate an objective method for the assessment of bradykinesia	Gyroscope, accelerometer, magnetometer, and EMG	Methods detected objective bradykinesia differences between PD and HC	Good
Jeon 2017	Cross-sectional	85 PD	Inc: PD with hand tremor Exc: leg tremor and dyskinesia	Assess automatic scoring system for PD tremor	Wearable sensor Gyroscope Accelerometer	Predicted UPDRS tremor scores with high accuracy	Good
Bologna 2016	Cross-sectional	18 PD 16 HC	Inc: PD Exc: dementia, neuropsychiatric disorders, facial movements or trauma	Assess deficits in facial emotional processing and recognition in PD	Optokinetic system	Altered emotional processing in PD not correlated to emotional recognition deficits	Good
Ricciardi, 2015	Cross-sectional	40 PD 17 HC	Inc: PD Exc: cognitive deficits, depression	Correlate reduced expressiveness and altered emotion processing in PD	Optokinetic system	Reduced facial expressiveness correlates with impaired emotional recognition.	Good
Muller 2010	Cross-sectional	27 PD 27 HC	Inc: PD patients Exc: motor fluctuations	Evaluate pronation and supination of forearm in PD vs. HC	Diadochokinometer	PD patients showed reduced maximum velocity, interval and amplitude	Good
Rand 2010	Cross-sectional	12 PD 12 HC	Inc: PD Exc: other neurological disease	Assess wrist and trunk kinematic parameters in PD vs. HC	Kinematic systems	PD considerably lengthened transport time, especially during the aperture closure period, and decreased peak velocity of wrist and trunk movement	Good

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2	Espay 2009	Cross-sectional	23 PD 16 HC	Inc: PD Exc: severe tremor, DBS, cognitive impairment, UMN/LMN signs, atypical parkinsonism	Categorize the spectrum of movements in PD in terms of speed and amplitude	Wearable motion sensor	Amplitude and speed impairments may be associated with different functional aspects in PD	Good
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8	Mak 2007	Cross-sectional	21 PD 21 HC	Inc: PD, H&Y 2 or 3, stable PD medication Exc: N/R	Develop an objective measure to quantify trunk rigidity i n PD	Force plate	Method differentiated trunk rigidity in PD versus HC. There were increases in work done and resistive peak torques upon motor tasks	Good
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13	Castiello 2000	Cross-sectional	14 PD 14 HC	Inc: PD patient; Right dominance Exc: Motor complications due to therapy	Evaluate reach-to-grasp movement in PD patients during ON and OFF states	Motion analysis	Dopaminergic medication reduced bradykinesia and fine-tuning kinematic movement during reach-to-grasp task	Good
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18	Lin 2018	Cross-sectional	15 ET 15 PD	Inc: ET or PD Exc: N/R	Quantify tremor spatially and temporally in PD	Tablet-based	Tablet measures of tremor correlates well with current clinical assessments	Fair
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23	Summa 2017	Cross-sectional	7 PD 7 HC	Inc: PD, H&Y 1 - 2.5 Exc: movement limitations for conditions other than PD	Analyze the kinematic and dynamic characteristics of goal- directed movements	Kinematic analysis	Prono-supination task is consistent to quantify bradykinesia with gyroscopes. Peak power seems appropriate for bradykinesia symptom evaluation.	Fair
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29	Heremans 2016	Cross-sectional	30 PD 15 HC	Inc: PD, H&Y 1 - 3 Exc: depression, neurological comorbidities	Assess writing quality in PD with and without FOG	Tablet-based	Patients with FOG showed decreased writing amplitudes and increased variability compared to HC and PD w/o FOG	Fair
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34	Fraiwan 2016	Cross-sectional	21 PD 21 HC	Inc: PD Exc: N/R	Detect and quantify hand tremor in PD	Acceleromete r	Detected hand tremor and diagnosed PD with high accuracy	Fair
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38	Van Gilst 2015	Case-control	36 PD w&w/o sleep benefit	Inc: PD Exc: psychiatric diagnosis, DBS, other neurological disease, hypnotics	Evaluate the influence of sleep on motor functioning in PD	PSG dexterity pegboard	Sleep benefit is not paralleled by an actual improvement in motor functioning	Fair
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Thanawattano 2015	Cross-sectional	22 ET 35 PD	Inc: ET or PD Exc: N/R	Assess tremor in time domain ('temporal fluctuation')	Wearable sensor gyroscope	Temporal fluctuation distinguishes tremor in PD and ET	Fair
Thanawattano 2015	Cross-sectional	32 PD 20 ET	Inc: PD or ET Exc: N/R	Quantify tremor fluctuation during resting and kinetic tasks in PD	Gyroscope	Tremor fluctuation can distinguish PD from ET tremor	Fair
Kotschet 2014	Cross-sectional	68 PD 30 HC	Inc: levodopa responsive PD Exc: N/R	Evaluate relationship between episodes of sleep immobility to bradykinesia, dyskinesia and daytime sleepiness	Accelerometer	Immobility is a marker of daytime sleep in PD	Fair
Cano-de-la-Cuerda, 2014	Cross-sectional	36 PD	Inc: PD with good walking ability Exc: Dementia, depression	Quantify trunk rigidity in PD	Dynamometer	Trunk rigidity correlates with disease severity, disease duration, functional status	Fair
Jobbágy 2004	Cross-sectional	10 PD 32 HC	Inc: N/R Exc: N/R	Evaluate finger-tapping in PD	Kinematic systems	Wearable sensor detected decreased amplitude of finger-tapping in PD	Fair
Fimbel 2003	Cross-sectional	18 PD 18 HC	Inc: PD, atypical parkinsonism, right handed Exc: neurological comorbidities	Assess a qualitative pattern-matching technique for detecting events in movement recordings	Motion analysis	Reaction time and movement length were similar in PD and HC, but PD reached lower maximum speeds longer execution times than HC.	Fair
Zeuner 2003	Cross-sectional	12 PD 11 ET 6 psychogenic	Inc: N/R Exc: N/R	Measure frequency changes during tapping	EMG	Absolute change in tremor frequency and marked intraindividual variability with tapping in psychogenic tremor	Fair
Kelly 2002	Cross-sectional	9 PD 9 HC	Inc: N/R Exc: N/R	Examine the impact of levodopa on the voluntary movements in PD	Kinematic systems	PD patients increase reach velocity and decrease movement time after taking levodopa	Fair

Martin 2002	Cross-sectional	12 PD 28 HC	Inc: PD; H&Y 1 to 3 Exc: acute illnesses, OH	Evaluate distance between the vertical projections of the COM and the COP to reflect postural control during gait initiation	Kinematic systems	PD patients allow less COM-COP distance than HC	Fair
Wenzelburger 2000	Cross-sectional	13 PD 12 HC	Inc: H&Y 1to 3, hand rest tremor Exc: N/R	Evaluate kinetic tremor (reach a target) in tremor-dominant PD	Accelerometer EMG Kinematic systems	Accelerometer detected greater frequency of kinetic tremor before the onset of the movement in PD	Fair
Johnson 1994	Cross-sectional	20 PD	Inc: N/R Exc: N/R	Examine the acute change in motor performance after Levodopa	Kinematic systems	Levodopa increase velocity in self-paced tasks	Fair
Svensonn 1993	Cross-sectional	9 PD 9 HC	Inc: PD Exc: Poor dental status	Analyze jaw movement characteristics in PD during the ON versus OFF motor state	Motion analysis	Motion analysis detected differences between ON and OFF motor states during a syllable repetition task	Fair
Popovic 2008	Cross-sectional	8 PD	Inc: PD Exc: N/R	Describe hand motor blocks in PD using a digitizing tablet	Tablet-based	Digitizing tablet can be used to record sudden discontinuations during planar movements in PD	Poor
Vaillancourt 2000	Cross-sectional	8 PD 8 HC	Inc: no clinical signs of tremor Exc: N/R	Examine tremor features in PD	Accelerometer EMG	PD tremor was more regular vs. physiological tremor in HC	Poor

PD, Parkinson’s disease; HC, Healthy control; Inc, Inclusion; Exc, Exclusion; w&w/o, with and without; N/R, non-reported; DBS, Deep brain stimulation; STN, Subthalamic nucleus; EMG, Electromyography; UMN, upper motor neuron; LMN, lower motor neuron; COM, center of mass; COP, center of pressure; H&Y, Hoehn & Yahr; FOG, freezing of gait

Table 3: Eligible Studies Assessing Cognitive Function and Speech

Study	Design	Population	Selection Criteria	Aim	Technology	Results	Quality
Godino-Llorente 2017	Cross-sectional	50 PD 50 HC	Inc: PD Exc: other neurological disorders	Assess speech biomarkers to evaluate PD	Speech analysis	Articulatory biomarkers accurately identify PD	Good
Vaiciukynas 2017	Cross-sectional	64 PD 35 HC	Inc: PD Exc: N/R	Assess sustained phonation for diagnosis of PD	Speech analysis	Acoustic analysis can accurately detect PD	Good
Markser 2015	Case-control	30 PD w&w/o cognitive impairment	Inc: DBS indication Exc: N/R	EEG metrics after DBS	EEG	STN-DBS has a negative effect on the patients grand total EEG scores	Good
Arora 2015	Cohort	10 PD 10 HC	Inc: PD Exc:N/R	Assess if symptom recordings can differentiate PD vs. HC	Tablet-based Speech analysis Gyroscope Accelerometer	PD symptoms can be feasibly measured via smartphone	Good
Nojszewska 2009	Cross-sectional	46 PD 14 HC	Inc: PD Exc: severe illness, deafness	Neuropsychological test relation determination to AEP	AEP	AEP of different latencies are helpful in the assessment of cognitive changes associated with PD.	Good
Tanaka 2018	Cross-sectional	137 PD	Inc: PD with ambulatory and OH data Exc: acute illnesses	Assess relationship between nocturnal BP and dementia in PD	24-hour ambulatory BP and heart rate	Nocturnal BP rise and OH correlated with dementia	Fair

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Gauvin 2017	Cross-sectional	18 PD 16 HC	Inc: PD Exc: other neurological disorders	Assessed verbal monitoring in PD	Speech analysis	PD has different verbal monitoring patterns and greater impairment vs. HC	Fair
Latreille 2016	Prospective cohort	68 PD 44 HC	Inc: PD Exclusion: dementia, stroke, epilepsy	Prediction of PDD by PSG	PSG	PD patients who developed PDD had higher slowing ratio in temporal, parietal, and occipital regions during REM sleep	Fair
Rektorova 2016	Cohort	44 PD	Inc: PD Exc: depression	Assessed relationship between speech impairment and cognitive decline	Speech analysis	Impairment of speech prosody predicted rapid cognitive decline	Fair
Zimmermann 2015	Cross-sectional	48 PD	Inc: PD Exc: dementia, stroke, epilepsy, low-quality EEG	Test EEG slowing relation to cognitive performance	EEG	Global EEG slowing is a marker for overall cognitive impairment and specific domains	Fair
Latreille 2015	Prospective cohort	68 PD w&w/o cognitive impairment 47 HC	Inc: PD Exc: dementia, stroke, epilepsy	Test PSG prediction of dementia	PSG	Sleep spindle alterations related to dementia development	Fair
Fischer 2010	Cross-sectional	10 PD 9 HC	Inc: English native speakers Exc: dementia, depression, serious illness, speech impairment	Examine voice onset measures in PD	Voice analysis	PD medication had an effect on voice onset time change	Fair
Fonseca 2009	Cross-sectional	32 PD 26 HC	Inc: PD Exc: antipsychotics, benzodiazepines	Evaluate relation between quantitative EEG and cognitive disturbance	EEG	EEG abnormalities were associated with mild cognitive impairment or dementia in PD versus HC	Fair
Matsui 2007	Cross-sectional	40 PD w&w/o dementia	Inc: H&Y 3 or 4 Exc: atypical parkinsonism	Examine P300 differences between PDD and PD	EEG	P300 latency was markedly delayed in PDD patients	Fair

Bunton 2005	Cross-sectional	7 PD 6 HC	Inc: PD, English native speaker Exc: dementia, hypoacusia	Determine patterns of lung volume use in PD during an extemporaneous speaking task	Microphone, magnetometer	Speakers with PD began speaking at lower lung volumes and had an increased variability in starting lung volumes across the speech sample versus HC	Fair
Katsarou 2004	Cross-sectional	45 PD 40 HC	Inc: PD, MMSE > 25, H&Y 2 to 3 Exc: dementia	Compare P300 between PD patients and HC	EEG	Non-demented PD patients had a prolonged P300 latency versus HC	Fair
Antal 2000	Cross-sectional	20 PD 20 ET 20 HC	Inc: PD or ET Exc: retinopathy, glaucoma, DM, alcoholism	Compare components of VEP in patients with PD and ET	VEP	No significant overall group difference	Fair
Hawkes 1997	Cross-sectional	37 PD 47 HC	Inc: PD, MMSE > 26, Exc: head trauma, DM, alcoholism	Evaluate olfactory function in PD	UPSIT, Olfactory evoked potentials	Over 70% of PD were abnormal. The evoked potentials were significantly delayed but comparable to HC.	Fair
Sagliocco 1997	Cross-sectional	17 PD 17 HC	Inc: PD, MMSE $\geq$ 23, visual acuity $\geq$ 20/40, Exc: unable to cooperate	Compare simultaneously recorded VEP and event related potentials in PD	VEP EEG	Simultaneous VEP and visual event related potentials recordings are helpful to distinguish younger PD patients from HC	Fair
Green 1996	Cross-sectional	20 PD 20 HC	Inc: PD Exc: depression	Understand P3-associated variability in PD	EEG	P3 amplitude may be more sensitive than neuropsychological measures for subtle brain dysfunction in early PD	Fair
Pekkonen 1995	Cross-sectional	13 PD 11 HC	Inc: PD Exc: severe illness, deafness	Determine stimulus change impairment in PD	EEG	Mismatch negativity of event-related potentials are smaller in PD versus HC	Fair
Okuda 1995	Case-control	32 PD 22 HC	Inc: visual acuity > 0.7 Exc: ophthalmological disease	Measure differences in VEP in PD, PDD, and HC	VEP	PDD has prolonged P100 latencies versus both non-demented PD and HC	Fair

Kim 1995	Cross-sectional	16 PD 15 HC	Inc: PD, MMSE > 24, Exc: antipsychotics, brain image lesion	Use P300 as index of cognitive function in PD	EEG	P300 was inversely correlated with performance of visuomotor procedural memory.	Fair
Peppe 1995	Cross-sectional	18 PD 8 HC	Inc: de novo PD Exc: DM, retinopathy	Determine VEP characteristics in de novo PD	VEP	PERG P50 and VEP P100 latencies were increased in de novo PD before therapy versus HC	Fair
Bodis-Wollner 1995	Cross-sectional	50 PD	Inc: PD Exc: dementia, thalamotomy, depression	Determine event related potentials characteristics in PD	EEG	Longer ERP latencies correlated to lower scores on tests of cognitive functioning.	Fair
Vierregge 1994	Cross-sectional	14 PD 16 HC	Inc: right handed Exc: depression, dementia, deafness	Assess selective auditory attention with processing negativity in PD	EEG	Processing negativity smaller in PD versus HC at a rate of 1 tone/second	Fair
Filipovic 2001	Cross-sectional	16 PD w&w/o depression	Inc: PD Exc: severe tremor, focal brain lesions	Determine readiness potential patterns that distinguish w&w/o depression	EEG	Readiness potentials amplitude and slopes were smaller in PD, but w/o specific patterns that differentiated w&w/o depression	Poor
Buttner 1996	Cross-sectional	39 PD 43 HC	Inc: PD Exc: dementia, retinopathy, daltonism	Assesss chromatic VEP in PD patient	VEP	VEP demonstrate dysfunction of the visual system in PD	Poor

PD, Parkinson’s disease; HC, Healthy control; Inc, Inclusion; Exc, Exclusion; w&w/o, with and without; N/R, non-reported; min, minutes; PDD, Parkinson’s disease dementia; PSG, Polysomnography; DBS, Deep brain stimulation; STN, Subthalamic nucleus; EEG, electroencephalography; VEP, Visual evoked potentials; AEP, Auditory evoked potentials; DM, Diabetes mellitus; HTN, Hypertension; & Yahr; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension; ERP, event related potential; UPSIT, Smell Identification Test

Table 4: Eligible Studies Assessing Sleep

Study	Design	Population	Selection Criteria	Aim	Technology	Results	Quality
Loo 2008	Prospective Case-control	200 PD 200 HC	Inc: newly diagnosed PD, MMSE > 24 Exc: N/R	Correlate RLS and PD	PSG	Weak association between RLS and PD	Good
Zibetti 2017	Prospective Cohort	11 PD	Inc: Levodopa carbidopa intestinal gel Exc: MMSE < 24	Evaluate the impact of gel infusion on sleep parameters	PSG	PSG showed less fragmented sleep pattern in PD patients treated with Levodopa carbidopa intestinal gel	Fair
Schroeder 2016	Case-control	50 PD 31 HC	Inc: early and mid-duration PD Exc: Dementia	Explore REM density in PD across disease duration	PSG	REM density is reduced in patients with mid-duration PD and correlates with subjective scores on sleep impairment	Fair
Alatriste-Booth 2015	Cross-sectional	120 PD	Inc: PD Exc: Insufficient sleep time	Sleep disorders prevalence in PD	PSG	Sleep apnea-hypopnea syndrome and RBD were the most frequent sleep disorders.	Fair
Valli 2015	Prospective cohort	15 PD w&w/o RBD	Inc: PSG recording Exc: Dementia, hallucinations	Test differences in dream content of PD patients w&w/o RBD	PSG	No differences in dream content of PD patients w&w/o RBD	Fair
Louter 2014	Case-control	45 PD w&w/o RBD	Inc: PD Exc: <10 min of REM sleep in PSG	Actigraphy as a diagnostic tool for RBD in PD patients	Actigraphy	PD patients w/RBD have more bouts scored as “wake” using actigraphy, compared to patients w/o RBD.	Fair
Vaughan 2013	Cross-sectional	60 PD	Inc: PD Exc: dementia, DBS, serious comorbidities	Clinical factors related to nocturia and sleep disruption	PSG	More episodes of nocturia associated with less total sleep time and efficiency	Fair

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2	Naismith 2010	Cross-sectional	22 PD w&w/o RBD	Inc: PD Exc: N/R	Evaluate actigraphy for RBD reported by PD patients	Actigraphy	PD patients w/RBD have higher number of wake bouts than PD patients w/o RBD	Fair
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6	Shpirer 2006	Prospective cohort	46 PD 30 HC	Inc: PD Exc: N/R	Compare sleep characteristics of PD versus HC	PSG	PD had lower sleep efficiency, longer Stage 2 sleep and shorter REM sleep	Fair
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11	Dhawan 2006	Cross-sectional	59 PD 131 HC	Inc: PD, H&Y 3 to 5 Exc: N/R	Compare sleep problems in untreated PD compared to advanced PD and HC	PSG	Advanced PD demonstrated PSG patterns of periodic limb movement of sleep, obstructive sleep apnea, and RBD	Fair
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15	Diederich 2005	Case-control	49 PD 49 HC	Inc: PD Exc: N/R	Nocturnal respiration impact on sleep continuity and architecture	PSG	In non-obese PD patients, sleep apnea syndrome is not a major cause for sleep fragmentation	Fair
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20	Gagnon 2004	Cross-sectional	15 PD	Inc: PD, H&Y 1 to 3 Exc: atypical parkinsonism, antidepressants, serious illness	Compare EEG of PD w&w/o RBD	EEG	EEG slowing reported during wakefulness in non-demented PD is strongly correlated to RBD	Fair
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25	Cicolin 2004	Cross-sectional	5 PD	Inc: PD undergoing DBS Exc: N/R	Evaluate sleep architecture modifications after STN DBS	PSG	STN DBS increases total sleep time and reduces wakefulness after sleep onset	Fair
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30	Moller 2002	Cross-sectional	6 PD	Inc: unusually fast or sudden onset of sleep, combined dopamine agonist + levodopa Exc: N/R	Investigate nighttime sleep quality and degree of daytime sleepiness in PD patients with sleep attacks	PSG	Unusually fast or sudden onset of sleep in PD patients is a phenomenon of daytime sleepiness	Fair
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36	Gagnon 2002	Cross-sectional	33 PD 16 HC	Inc: H&Y 1 to 3, use of dopamine agonists Exc: atypical signs for PD diagnosis	Determine the frequency of RBD among patients with PD	PSG	A third of patients with PD meet RBD criteria based on PSG, but only half of these cases would have been detected by history taking.	Fair
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Young 2002	Cross-sectional	18 PD	Inc: PD, Epworth scale ≥ 8 Exc: H&Y 3	Determine the effect of mild versus severe PD on sleep parameters	PSG	There was no significant difference in objective sleep parameters between the two groups.	Fair
Comella 1993	Cross-sectional	10 PD	Inc: L-dopa + dopamine agonist for ≥ 6 months Exc: dementia, depression, serious illness	Compare PSG in PD with and without hallucinations	PSG	The hallucinator group had a lower sleep efficiency, a reduced total REM sleep time, and a reduced REM percentage	Fair
Perez-lloret 2009	Cross-sectional	71 PD 21 HC	Inc: PD, MMSE > 24 Exc: N/R	Correlate sleep logs compared to PD Sleep Scale	Actigraphy	Retrospective sleep quality evaluation by the PDSS and day-to-day evaluation by sleep log coincided	Poor
Norlinah 2009	Cross-sectional	51 PD	Inc: PD Exc: active psychiatric condition, benzodiazepine, sedative or excessive alcohol use	Determine the prevalence of sleep disorders in PD	PSG	The prevalence of PSG-quantified sleep disturbances is high. Sleep fragmentation is the most common	Poor
Moller 2009	Case-control	14 PD w&w/o sleep attack	Inc: PD, sudden sleep onset Exc: N/R	Characterize and analyze sleep attack patterns on EEG	EEG	Sleep attacks are characterized by NREM stage 1 and 2 sleep in daytime EEG	Poor
Diederich 2009	Cross-sectional	62 PD	Inc: PD, sleep complaints Exc: Dementia	Examine the influence of diurnal dopaminergic medication on sleep	PSG	No impact of diurnal dopaminergic medication on nocturnal slow-wave sleep in PD patients	Poor
Uemura 2009	Cross-sectional	79 PD 79 HC	Inc: PD Exc: atypical parkinsonism	Examine the relation between the PD sleep scale and PSG	PSG	PD sleep scale had significant correlation with PSG-measured sleep efficiency.	Poor
Roth 2003	Case-control	16 PD w&w/o sleep episodes	Inc: H&Y 1 to 3, use of dopamine agonists Exc: serious comorbidities	Determine the association of dopamine agonists, daytime sleepiness, and sleep episodes	PSG	Sleep episodes are related with excessive daytime sleepiness and unrelated to nocturnal sleep or use of any specific dopamine agonist	Poor

PD, Parkinson’s disease; HC, Healthy control; Inc, Inclusion; Exc, Exclusion; w&w/o, with and without; N/R, non-reported; PSG, Polysomnography; REM, Rapid eye movement; DBS, Deep brain stimulation; STN, Subthalamic nucleus; EEG, electroencephalography; RBD, REM-sleep behavior disorder; H&Y, Hoehn & Yahr; MMSE, Mini-Mental State Examination

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Table 5: Eligible Studies Assessing Autonomic Function

Study	Design	Population	Selection Criteria	Aim	Technology	Results	Quality
Pavy-LeTraon 2018	Cross-sectional	62 MSA-P 96 PD	Inc: PD or MSA-P Exc: N/R	Differentiate MSA from PD	Cardiovascular and sweating autonomic testing	Cardiovascular and sweating tests are useful for differentiating MSA-P and PD	Good
Vichayanrat 2017	Cross-sectional	23 MSA 18 PD w/ autonomic failure 33 PD w/o AF	Inc: PD or probable MSA with OH Exc: other illnesses that affect autonomic function	Assess 24 hour ambulatory blood pressure compared to head-up tilting for diagnosing OH in PD and MSA	24 hour ambulatory BP and heart rate	Standing test during 24 hour ambulatory BP had high accuracy in diagnosing OH	Good
Merola 2017	Cross-sectional	30 PD w/ STN-DBS 30 PD w/ LCIG	Inc: PD Exc: N/R	Assess dysautonomia in PD with STN DBS or LCIG	Cardiovascular autonomic testing	Dysautonomia affected patients with STN DBS and LCIG equally	Good
De Pablo-Fernandez 2017	Cross-sectional	100 PD	Inc: PD from autopsy Exc: atypical Parkinsonisms and other illnesses	Correlate onset of autonomic dysfunction with progression and survival	Autonomic function testing (urinary/ED, GI, cardiovascular, and sweating)	Earlier autonomic dysfunction onset correlates with rapid progression and shorter survival	Fair
Baschieri 2015	Cross-sectional	34 MSA-P 65 PD 38 HC	Inc: PD or MSA-P Exc: other illnesses that affect autonomic function	Differentiate MSA from PD	Cardiovascular autonomic testing	Cardiovascular tests are useful for differentiating MSA-P and PD at an early stage	Fair

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Haapaniemi 2001	Cross-sectional	54 PD 47 HC	Inc: treatment-naïve PD Exc: autonomic dysfunction	Examine autonomic cardiovascular regulation in untreated PD	24-hour ECG monitoring	Patients with mild hypokinesia had higher heart frequency than patients with more severe hypokinesia.	Fair
Tanaka 2000	Cross-sectional	29 PD 11 HC	Inc: PD Exc: atypical parkinsonism, depression	Compare the P3 and N1 amplitude between demented, non-demented PD, and HC	EEG	There was an increased P3 amplitude and EEG power in non-demented PD patients versus controls	Fair
Oka 1997	Cross-sectional	30 PD 30 HC	Inc: PD, H&Y 1 to 4 Exc: atypical parkinsonism, antiparkinsonian drugs other than L-dopa/carbidopa	Evaluation of QTc interval in patients with PD versus HC	ECG	QTc intervals in PD significantly longer than in HC. Unrelated to administration of levodopa	Fair
Oka 2003	Cross-sectional	20 PD 50 HC	Inc: N/R Exc: N/R	Evaluation of R-R interval and BP during Valsava maneuver and deep inspiration	ECG, continuous BP monitoring	Baroreflex sensitivity in PD is smaller than in HC	Poor
Mastrocola 1999	Cross-sectional	13 PD 13 HC	Inc: PD Exc: DM, HTN, drugs affecting autonomic tone	Evaluate autonomic dysfunction in PD	24-hour ECG monitoring	Significant difference in ECG parameters between PD and HC, reflecting a reduction in autonomic function.	Poor

PD, Parkinson’s disease; HC, Healthy control; Inc, Inclusion; Exc, Exclusion; w&w/o, with and without; N/R, non-reported; min, minutes; PDD, Parkinson’s disease dementia; DBS, Deep brain stimulation; STN, Subthalamic nucleus; EEG, electroencephalography; ECG, Electrocardiography; DM, Diabetes mellitus; HTN, Hypertension; LCIG, levodopa-carbidopa infusion gel; MSA and MSA-P, Multiple System Atropy – Parkinsonism; OH, orthostatic hypotension; BP, blood pressure; H&Y, Hoehn and Yahr

Table e-1: Database search methods

Pubmed
Search term (filter humans, English)
<p>("Parkinson Disease"[Mesh] AND parkinson's OR parkinson OR parkinson's disease) AND (smartphone OR "Smartphone"[Mesh] OR iphone OR sensor OR palms OR personal digital assistant OR "Computers, Handheld"[Mesh] OR PDA OR accelerometer OR accelerometry OR "Accelerometry"[Mesh] OR computer OR "Computers"[Mesh] OR "Therapy, Computer-Assisted"[Mesh] OR "Signal Processing, Computer-Assisted"[Mesh] OR "Diagnosis, Computer-Assisted"[Mesh] OR "Decision Making, Computer-Assisted"[Mesh] OR "Computer Systems"[Mesh] OR microcomputers OR "Microcomputers"[Mesh] OR PC OR desktop OR laptop OR tablets OR ipad OR digital OR "Cell Phone"[Mesh] OR "Software"[Mesh] OR stylus OR electronic OR "Electronics"[Mesh] OR interface OR computer interface OR brain-computer interface OR "Brain-Computer Interfaces"[Mesh] OR user-computer interface OR "User-Computer Interface"[Mesh] OR gait analysis OR gait OR "Gait"[Mesh] OR gyroscope OR microphone OR "Transducers"[Mesh] OR voice analysis OR speech analysis OR voice OR speech OR "Speech Recognition Software"[Mesh] OR stride walk OR "Walking"[Mesh] OR gait mat OR gait rite OR actigraphy OR "Actigraphy"[Mesh] OR actigraph OR smartwatch OR barometer OR wearable sensors OR wearables OR "Wearable Electronic Devices"[Mesh] OR wireless device OR wireless OR "Wireless Technology"[Mesh] OR device OR "Equipment and Supplies"[Mesh] OR wifi OR internet OR "Internet"[Mesh] OR radios OR "Radio"[Mesh] OR battery OR monitor OR "Monitoring, Physiologic"[Mesh] OR blue tooth OR LED OR LCD OR display OR "Data Display"[Mesh] OR touchscreen OR camera OR video camera OR motion sensor OR gait trolley OR treadmill OR apps OR applications OR "Mobile Applications"[Mesh] OR "Medical Informatics Applications"[Mesh] OR tilt table OR "Tilt-Table Test"[Mesh] OR facial recognition software OR heart rate monitor OR pulse OR sweat monitor OR cantab OR PSG OR polysomnography, AND "Polysomnography"[Mesh] OR light sensor OR oximeter OR EEG OR electroencephalography OR "Electroencephalography"[Mesh] OR ECG OR EKG OR electrocardiogram OR "Electrocardiography"[Mesh] OR EMG OR electromyography OR "Electromyography"[Mesh] OR cpap OR continuous positive airway pressure OR "Continuous Positive Airway Pressure"[Mesh] OR blood pressure monitor OR "Blood Pressure Monitors"[Mesh] OR electronic diary OR e-diary OR evoked potentials OR upset OR university of pennsylvania smell identification test OR pedometer OR fitbit OR kinematic OR "Biomechanical Phenomena"[Mesh] OR imus OR inertial measurement units) NOT (review article OR "Review"[Publication Type] OR msa OR multiple system atrophy OR "Multiple System Atrophy"[Mesh] OR "Parkinson Disease, Secondary"[Mesh] OR atypical parkinsonism OR psp OR progressive supranuclear palsy OR "Supranuclear Palsy, Progressive"[Mesh] OR "Tauopathies"[Mesh] OR "Lewy Body Disease"[Mesh] OR lewy body dementia OR lewy body disease OR vascular parkinsonism OR "Molecular Imaging"[Mesh] OR "Multimodal Imaging"[Mesh] OR "Cardiac Imaging Techniques"[Mesh] OR "Diffusion Tensor Imaging"[Mesh] OR "Diagnostic Imaging"[Mesh] OR "Magnetic Resonance Imaging"[Mesh] OR MRI OR magnetic resonance imaging OR magnetic resonance OR ct OR computerized tomography OR "Tomography"[Mesh] OR blood analysis OR "Hematologic Tests"[Mesh] OR csf OR cerebrospinal fluid OR "Cerebrospinal Fluid"[Mesh] OR wolff-parkinson-white syndrome OR "Wolff-Parkinson-White Syndrome"[Mesh])</p>

Quality Rating Assessment for Case-control studies													
	1	2	3	4	5	6	7	8	9	10	11	12	Quality Rating
Markser 2015	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y	Good
Loo 2008	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	N	Good
Schroeder 2016	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	N	Fair
Heremans 2016	Y	Y	N	Y	Y	Y	N	Y	N	Y	N	N	Fair
Van Gilst 2015	Y	Y	N	Y	Y	Y	N	Y	N	Y	N	N	Fair
Valli 2015	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y	Fair
Latreille 2015	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y	Fair
Chomiak 2015	Y	Y	N	Y	Y	Y	N	Y	N	Y	N	N	Fair
Louter 2014	Y	Y	N	Y	Y	Y	N	Y	N	Y	N	N	Fair
Barbe 2014	Y	Y	N	Y	Y	Y	N	Y	N	Y	N	N	Fair
Fonseca 2009	Y	Y	N	Y	N	Y	N	Y	N	Y	Y	N	Fair
Diederich 2005	Y	Y	N	Y	N	Y	N	Y	N	Y	N	N	Fair
Okuda 1995	Y	Y	N	Y	Y	Y	N	Y	N	N	N	N	Fair
Comella 1993	Y	Y	N	Y	Y	Y	N	Y	N	Y	Y	Y	Fair
Moller 2009	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	N	Poor
Filipovic 2001	Y	Y	N	Y	Y	Y	N	Y	N	N	N	N	Poor

Questions:

1. Was the research question or objective in this paper clearly stated and appropriate?
2. Was the study population clearly specified and defined?
3. Did the authors include a sample size justification?
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?

6. Were the cases clearly defined and differentiated from controls?
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?
8. Was there use of concurrent controls?
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?
11. Were the assessors of exposure/risk blinded to the case or control status of participants?
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?

Quality Rating Assessment – Observational cohort and cross-sectional studies															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality Rating
Pavy-LeTraon 2018	Y	Y	N	Y	N	Y	Y	N	N	Y	Y	N	Y	Y	Good
Rabelo 2017	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Schlachetzki 2017	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Son 2017	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Conradsson 2017	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	Y	N	Good
Vichayanrat 2017	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Merola 2017	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Good
Godino-Llorente 2017	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Vaiciukynas 2017	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Pham 2017	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	Y	Good
Bologna 2016	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	Y	Y	Y	Good
Pasluosta 2015	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Good
Ricciardi 2015	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	Y	Y	Y	Good
Arora 2015	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Muller 2010	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Rand 2010	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Cho 2009	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Nojszewska 2009	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	Good
Švehlík 2009	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Mcvey 2009	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Kim 2009	Y	Y	N	N	N	Y	Y	Y	Y	N	Y	N	Y	N	Good
Espay 2009	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Alice 2007	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Mak 2007	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Hong 2007	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Good
Ferrarin 2005	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good
Stolze 2001	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	Y	Y	Good

Castiello 2000	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Good
Lin 2018	Y	N	N	N	N	Y	Y	N	Y	N	Y	Y	Y	N	Fair
Tanaka 2018	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Summa 2017	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Zibetti 2017	Y	Y	N	Y	N	Y	Y	N	Y	Y	Y	N	Y	N	Fair
Jeon 2017	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
De Pablo- Fernandez 2017	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	Y	Y	N	Fair
Gauvin 2017	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Latreille 2016	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Heremans 2016	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Fraiwan 2016	Y	Y	N	N	N	Y	Y	N	N	N	Y	Y	Y	Y	Fair
Rektorova 2016	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Alatriste-Booth 2015	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Zimmermann 2015	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Parisi 2015	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Thanawattano 2015	Y	Y	N	N	N	Y	Y	N	Y	N	Y	Y	Y	N	Fair
Thanawattano 2015	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Baschieri 2015	Y	Y	N	Y	N	N	Y	N	Y	Y	Y	Y	Y	N	Fair
Kotschet 2014	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Dillmann 2014	Y	N	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Cano-de-la- Cuerda 2014	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Vaughan 2013	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Moore 2013	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
WS Coriolano 2012	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Zampieri 2011	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Merello 2010	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	Fair

Salarian 2010	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Naismith 2010	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Ganesan 2010	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Fischer 2010	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	Fair
Johnsen 2010	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	N	Y	Fair
Cantinaux 2010	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	Y	Y	Fair
Mancini 2009	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Hong 2009	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Stack 2008	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Huxham 2008	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Carpinella 2007	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Matsui 2007	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Shpirer 2006	Y	Y	N	Y	N	Y	Y	N	Y	Y	Y	N	Y	N	Fair
Dhawan 2006	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Jobbagy 2004	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Gagnon 2004	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	Fair
Bunton 2004	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Katsaro 2004	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Cicolin 2004	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	Y	Fair
Roth 2003	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Fimbel 2003	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Zeuner 2003	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Kelly 2002	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Martin 2002	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	Y	Fair
Young 2002	Y	Y	N	Y	N	Y	Y	Y	Y	N	N	N	Y	N	Fair
Moller 2002	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Gagnon 2002	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Ferrarin 2002	Y	Y	N	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Fair
Haapaniemi 2001	Y	Y	N	Y	N	Y	Y	N	Y	N	N	N	Y	N	Fair
Wenzelrburger 2000	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Antal 2000	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair

Tanaka 2000	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Van Emmerik 1999	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Fair
Oka 1997	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Hawkes 1997	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Sagliocco 1997	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Green 1996	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Kim 1995	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Peppe 1995	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Bodis-Wollner 1995	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Pekkonen 1995	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Johnson 1994	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Vieregge 1994	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Fair
Svensonn 1993	Y	Y	N	Y	N	N	Y	N	Y	N	Y	N	Y	N	Fair
Doan 2010	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Poor
Uemura 2009	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	Poor
Diederich 2009	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Poor
Perez-lloret 2009	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Poor
Norlinah 2009	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Poor
Popovic 2008	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Poor
Bleuse 2008	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Poor
Oka 2003	Y	N	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Poor
Vaillancourt 2000	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	Poor
Mastrocola 1999	Y	Y	N	Y	N	Y	Y	N	Y	Y	Y	N	Y	N	Poor
Buttner 1996	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	N	Poor

Questions

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?

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- 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
- 5. Was a sample size justification, power description, or variance and effect estimates provided?
- 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
- 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
- 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
- 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
- 10. Was the exposure(s) assessed more than once over time?
- 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
- 12. Were the outcome assessors blinded to the exposure status of participants?
- 13. Was loss to follow-up after baseline 20% or less?
- 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?