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ERICKSON OLIVEIRA MENEZES

NÃO HÁ PADRÃO PARA CARACTERIZAR A DOR EM PACIENTES COM DOENÇA DE PARKINSON: REVISÃO SISTEMÁTICA E META-ANÁLISE

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Orientadora: Profa. Dra. Josimari Melo DeSantana

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Aprovado em 24/02/2023

Profa. Dra. Josimari Melo DeSantana
Universidade Federal de Sergipe

Prof. Dr. Eduardo Luis de Aquino Neves
Universidade Federal de Sergipe

Profa. Dra. Isabela Azevedo Freire Santos
Universidade Federal de Sergipe

PARECER

Dedico esta dissertação aos meus pais, que incentivaram e apoiaram os meus estudos.

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Arrisque sempre mais do que a maioria;
sonhe sempre mais alto do que os outros.
Howard Schults

RESUMO

Não há padrão para caracterizar a dor em pacientes com doença de Parkinson: revisão sistemática e meta-análise, Erickson Oliveira Menezes, 2023.

Introdução: A doença de Parkinson (DP) é uma doença crônica e degenerativa com sintomas motores e não motores. A dor como um dos principais sintomas não motores e as suas principais características ainda não estão esclarecidas. **Objetivo:** Caracterizar a dor em pessoas com doença de Parkinson. **Método:** Foram incluídos estudos observacionais, transversal e longitudinais, caso-controle e de coorte, realizadas na população com DP. As buscas ocorreram em 9 bases de dados para encontrar artigos que atendessem aos critérios deste estudo. O instrumento utilizado para avaliar a qualidade metodológica dos artigos incluídos foi o publicado pelo National Heart, Lung and Blood Institute (NHLBI). **Resultado:** Foram encontrados 14.197 artigos, dos quais foram selecionados 94 (28 do tipo caso-controle e 66 do tipo coorte e transversal, dos quais englobaram uma análise de 24.593 pessoas com DP e 5.626 controles. Trinta instrumentos diferentes foram usados para avaliar a dor em pessoas com DP. Dentre as principais características da dor, verificou-se que a maioria das pessoas com DP sente dores musculoesqueléticas, de intensidade moderada a intensa, principalmente na região das costas, que possivelmente é o sintoma inicial da DP e intensifica com o agravamento da doença e há alívio com terapia medicamentosa antiparkinsoniana. **Conclusão:** Esta revisão sistemática destaca que não há um padrão para caracterizar a dor em pessoas com DP, visto que é um sintoma presente na maioria desta população, mas não existem instrumentos suficientemente específicos e sensíveis para determinar e quantificar estas características em comparação a diferentes controles.

Palavras-chave: Doença de Parkinson, Dor, Medição da Dor**.**

ABSTRACT

There is no standard for characterizing pain in patients with Parkinson's disease: a systematic review and meta-analysis, Erickson Oliveira Menezes, 2023.

Introduction: Parkinson's disease (PD) is a chronic and degenerative disease with motor and non-motor symptoms. The pain as one of the main non-motor symptoms and its main characteristics are not yet clarified. **Objective:** To characterize pain in people with Parkinson's disease. **Method:** Observational, cross-sectional, longitudinal, case-control and cohort studies in the PD population were included. The searches took place in 9 databases to find articles that met the criteria of this study. The instrument used to evaluate the methodological quality of the included articles was published by the National Heart, Lung and Blood Institute (NHLBI). **Result:** A total of 14.197 articles were found, of which 94, 28 of the case-control type and 66 of the cohort and cross-sectional type were selected, of which they included an analysis of 24,593 people with PD and 5,626 controls. Thirty different instruments were used to assess pain in people with PD. Among the main characteristics of pain, it was found that most people with PD experience musculoskeletal pain, of moderate to intense intensity, especially in the back region, which is possibly the initial symptom of PD and intensifies with the worsening of the disease. disease and there is relief with antiparkinsonian drug therapy. **Conclusion:** This sysystematic review highlights that there is no pattern to characterize pain in people with PD since it is a symptom present in most of this population, but there are not sufficiently specific and sensitive instruments to determine and quantify these characteristics compared to different controls.

Key words: Parkinson disease, Pain, Pain Measurement.

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LISTA DE ABREVIAÇÕES E SIGLAS

AVD's – Atividades de vida diária

BDI – Inventário de Depressão de Beck;

BPI – *Brief Pain Inventory*

BVS – Biblioteca Virtual da Saúde

C&A – *Camptocormia e Antecollis*;

DASS – Escala de Ansiedade e Estresse de Depressão;

DEXA – Absortometria de Raio-X de Dupla Energia;

DMS-III – Manual Diagnóstico e Estatístico de Transtornos Mentais;

DP – Doença de Parkinson

ECN – Escala de Classificação Numérica

END – Escala Numérica da Dor

ESS – Escala de sonolência de Epworth;

EVA – Escala Visual Analógica

EVN – Escala Visual Numérica;

FACS – *Facial Action Coding System*

FOG-Q – Questionário de Congelamento da Marcha;

HADS – Escala Hospitalar de Ansiedade e Depressão;

HAMA – Escala de Classificação de Ansiedade de Hamilton;

HAND – Escala de Classificação de Depressão de Hamilton;

IASP – *Internacional Association for the Study of Pain*

K-MMSE – Versão Coreana do Mini Exame do Estado Mental;

K-PDQ-39 – Versão Coreana do Questionário de Doença de Parkinson;

KPPS – *King's Parkinson Disease Pain Scale*

LANSS – Avaliação de *Leeds* de Sintomas e Sinais Neuropáticos

LDP – Limiar de Dor por Pressão;

LEED – Dose Equivalente de Levodopa.

MA – Maior Depressão;

MADRS – Escala de Avaliação de Depressão de Montgomery-Åsberg;

MAIMS – Escala de Movimento Involuntário Anormal Modificado;

MDS-UPDRS-I – Escala de Avaliação da Doença de Parkinson Unificada da Sociedade de Distúrbios do Movimento Parte I

MEDLINE-PUBMED – Biblioteca Nacional da Saúde

MI – Menor Depressão;

MMII – Membros Inferiores

MMSE – Mini Exame do Estado Mental;

MMSS – Membros Superiores

MNSI – Instrumento de Triagem de Neuropatia de Michigan;

MoCA – Avaliação Cognitiva de Montreal Versão Pequim;

Questionário de McGill – *McGill* Pain Questionary

NFR – Reflexo de Flexão Nociceptiva;

NHLBI – *National Heart, Lung and Blood Institute*

NHP – Perfil de Saúde de *Nottingham*;

NMSQT – Questionário de Sintomas Não-Motores para pacientes com doença de Parkinson

NMSS – Escala de Sintomas Não Motores

NO – Sem Depressão;

NWDS – Escala de Deficiência de Northwestrn;

ODI – Índice de Incapacidade de Oswestry

PACA – Avaliação de Cuidados Paliativos;

PANAS – Cronograma de Afeto Positivo e Negativo;

PDI – Índice de Incapacidade de Dor

PDQ-39 – *Parkinson Disease Questionnaire–39*

PDQ-8 – Questionário da Doença de Parkinson com oito dimensões;

PDSS – Escala de sono da Doença de Parkinson;

PDYS-26 – Escala de Discinesia de Doença de Parkinson de 26 itens;

PFS-16 – Escala de Fadiga de Doença de Parkinson;

PIB – Produto Interno Bruto

PRISMA – *The Preferred Reporting Itens for Sytematic Reviews and Meta-Analyses*

PROSPERO – *International Prospective Register of Syistematic Reviews*

OS – Síndrome de *Pisa*;

PSE – Exame do Presente Estado;

PSQI – Índice de Qualidade do Sono de Pittsburg;

QVRS – Qualidade de Vida Relacionada a Saúde;

REM – *Rapid Eye Moviment Sleep*

RMF – Ressonância Magnética Funcional;

SF-12v2 – *Short-Form-12*

SF-36 – Estudo de Resultados Médicos 36—Formulário Resumido do Item

SFMPQ – Questionário de Dor de *McGill*-Forma Curta;

SMs – Sintomas Motores

SNMs – Sintomas Não Motores

SPI – Síndrome das Pernas Inquietas;

SQ – Questionário do Sono;

TUG – Teste *Timed UP and Go*;

UPDRS – Escala Unificada de Avaliação da Doença de Parkinson;

WAIS-III – Escala *Wechsler* de Inteligência para Adultos;

WMS-III: Escala de Memória *Wechsler*;

WOQ-9 – Questionário de Desgaste de 9 sintomas

WOS – *Web of Science*

WS – Sensação de Calor:

SUMÁRIO

1. INTRODUÇÃO

A doença de Parkinson (DP) é caracterizada como uma doença crônica, degenerativa e progressiva. Descrita pela primeira vez em 1817 por James Parkinson como paralisia agitante, ela é considerada a forma mais comum dos distúrbios de movimento e a segunda doença neurodegenerativa mais frequente no mundo, logo após a doença de Alzheimer (JANKOVIC, 2008; LUQUIN et al., 2017; SCHRAG et al., 2015; XIA; MAO, 2012). Nesta doença, ocorre uma degeneração progressiva dos neurônios dopaminérgicos nigroestriatais, ocasionando em alterações tônicas, posturais e de mobilidade (AL-JARRAH et al., 2007).

Mundialmente, estudos apontam que cerca de 2% da população mundial com idade acima de 60 anos tem a DP. No Brasil, a incidência é cerca de 3,3% da população acima dos 64 anos, 8,5% para as pessoas entre 80 e 85 anos e 14,3% para os indivíduos acima dos 85 anos (BOVOLENTA; FELICIO, 2017; CAMPOS et al., 2015; MONTEIRO et al., 2014; SILVA; CARVALHO, 2019; SOUZA et al., 2011). Ainda não está muito bem esclarecida a sua etiologia, mas acredita-se que cerca de 20% dos casos são determinados por fatores genéticos e/ou hereditários e 80% por fatores idiopáticos ou esporádicos (CURY et al., 2020; ROMO-GUTIÉRREZ et al., 2015).

Quatro sinais constituem os principais sintomas da DP, são chamados de sintomas motores (SMs), são eles: o tremor, a bradicinesia, a instabilidade postural e a rigidez muscular (SOUNDY; STUBBS; ROSKELL, 2014). Além dos SMs, existem outros sintomas que também estão associados, a exemplos de alterações cognitivas, fadiga, ansiedade, distúrbios gastrointestinais, dor, disfunções respiratórias e distúrbios do sono. Esses outros sintomas são caracterizados como sintomas não motores (SNMs) (FARNIKOVA; KROBOT; KANOVSKY, 2012).

Os SNMs já estão presentes desde o início da doença em, aproximadamente, 21% das pessoas com DP (TOLOSA; COMPTA; GAIG, 2007). Dentre estes sintomas, a dor é um dos mais frequentes e debilitantes, sendo relatada por cerca de 50 a 85% dos casos nesta população (BROEN et al., 2012; CURY et al., 2020; GREENBAUM et al., 2012; LUDWIG, 2008; MORENO et al., 2012). A dor está relacionada a qualidade de vida de maneira inversamente proporcional (CERRI; MUS; BLANDINI, 2019ª; QUITTENBAUM; GRAHN, 2004ª). Além disso, este sintoma é mais prevalente em mulheres e, também, está relacionado ao agravamento da doença, ou seja, quanto mais avançado o estadiamento da doença, a pessoa com DP relatará dor de maneira mais

intensa (VALKOVIC et al., 2015[a]). Na DP, há um distúrbio na produção e regulação de dopamina, que pode estar relacionado a uma hipersensibilização do sistema nervoso central, causando alteração na modulação nociceptiva frente a estímulos dolorosos, resultando na diminuição do limiar de dor e, consequentemente, maior sensibilidade a dor (BATTISTA; MEDICINE; 1973, [s.d.]; GERDELAT-MAS; …; 2007, [s.d.]; MORENO et al., 2012; RANA et al., 2013c; SUNG et al., 2018).

Nesta doença a dor pode ser classificada de maneira cronológica como aguda ou crônica, onde a primeira está descrita como um sintoma que dure em até 3 semanas e a segunda como uma dor que persiste ou se repete por três meses ou mais (LAWAND et al., 2015; NICHOLAS et al., 2019). Além disso, a dor pode ser de origem primária que é definida como dor em uma ou mais regiões anatômicas que persiste ou recorre por mais de 3 meses, está associada a sofrimento emocional significativo (por exemplo, ansiedade, raiva, frustração ou humor deprimido) e/ou incapacidade funcional significativa (interferência nas atividades da vida diária e participação em papéis sociais), e os sintomas não são melhor explicados por outro diagnóstico, ou de origem secundária que é quando este sintoma deriva de um outro diagnóstico (NICHOLAS et al., 2019).

Dor crônica foi notada na DP desde sua descrição original em 1817 por James Parkinson nos membros superiores (MMSS) e acredita-se que há a intensificação deste SNMs no período *off* do tratamento dopaminérgico, possibilitando uma correlação do sistema dopaminérgico com a nocicepção central desta população (EDINOFF et al., 2020). A dor pode modular predominantemente o controle motor, influenciando as áreas cognitivas, perceptivas e motoras de ordem superior do cérebro, e quando ela está presente em pessoas com distúrbios do movimento o controle motor pode estar deficitário (KANTAK; JOHNSON; ZARZYCKI, 2022).

Em geral, existem três mecanismos principais de dor na DP: dor nociceptiva, neuropática e nociplástica. O primeiro surge de dano real ou ameaçado ao tecido não neural e se dá devido à ativação de nociceptores, o segundo é causada por uma lesão ou doença do sistema nervoso somatossensorial, e por fim o terceiro surge da nocicepção alterada, apesar de não haver evidência clara de dano tecidual real ou potencial, causando a ativação de nociceptores periféricos ou evidência de doença ou lesão do sistema somatossensorial que causa a dor (MYLIUS et al., 2021; RAJA et al., 2020; SILVERDALE et al., 2018a).

Apesar de já existir alguns estudos que avaliaram a dor em pessoas com DP, ainda não estão esclarecidas quais as características dessa dor, mesmo após mais de 200

anos desde as primeiras descrições da doença, principalmente no que diz respeito à intensidade, localização, fatores de alívio e agravamento, cronologia da manifestação deste sintoma e ao tipo de mecanismo. Para que seja determinado o tratamento mais adequado para a dor em pessoas com DP, é necessário a compreensão com evidência científica deste sintoma.

2. REVISÃO DE LITERATURA

2.1. Conceito e histórico da doença de Parkinson

A doença de Parkinson (DP) é uma doença neurodegenerativa progressiva complexa definida pela perda de neurônios dopaminérgicos da substância negra, localizada no mesencéfalo e associada a corpos de Lewy (CERRI; MUS; BLANDINI, 2019b; HARRIS; LEENDERS; DE JONG, 2016; M et al., 2014). No entanto, a DP é caracterizada por uma patologia mais disseminada em outras regiões do cérebro e, também, envolve neurônios não dopaminérgicos (SIMON; TANNER; BRUNDIN, 2020). O diagnóstico clínico da DP é baseado principalmente nos SMs como tremor de repouso, rigidez, instabilidade postural e bradicinesia, embora os SNMs como distúrbios gastrointestinais, ansiedade, depressão, distúrbio do sono, fadiga e dor, possam se desenvolver anos antes das características motoras (PICILLO et al., 2014; SUNG; NICHOLAS, 2013).

A DP foi descrita pela primeira vez como uma doença neurológica em 1817 pelo médico britânico James Parkinson, onde foi registrado como principais sintomas os movimentos tremulantes involuntários, a perda de força muscular, a anteriorização do tronco e alteração de marcha, além disso foi observado que estes sinais eram progressivos (DEL REY et al., 2018; GOETZ, 2011; PARKINSON, 2002). Jean-Martin Charcot, em 1872, analisou de maneira mais minuciosa a DP e todos os seus sintomas, e a descreveu em dois tipos: a forma tremulante e a forma rígida/acinética. Ele também retrata a bradicinesia como sintoma mais prevalente e foi o primeiro a sugerir que esta doença fosse chamada de Doença de Parkinson (GOETZ, 2011). Anos depois, Willian Gower, estudou cerca de 80 casos de pessoas com DP, onde observou que era uma enfermidade que normalmente tem início após a meia-idade e apresentada em ambos os sexos, porém com uma prevalência em homens (GOWERS, 1887).

Em 1895, um estudo anatômico descreveu que pessoas com DP possuíam danos estruturais na substância negra e a partir disso o mesencéfalo se tornou o foco dos estudos patológicos desta doença (BRISSAUD, 1895). No entanto, apenas em 1997 foi observada a presença da mutação da alfa-sinucleína como uma das principais causas da DP (BRAAK et al., 2003; POLYMEROPOULOS et al., 1997). Hoehn e Yahr estudaram amplamente a progressão clínica desta doença e desenvolveram uma maneira de avaliar o estadiamento da DP de acordo com os sinais e sintomas presentes, dividindo em cinco estágios: estágio I, envolvimento apenas unilateral, geralmente com comprometimento

funcional mínimo ou inexistente; estágio II, envolvimento bilateral ou na linha média, sem comprometimento do equilíbrio; estágio III, primeiro sinal de reflexo de endireitamento prejudicado, os pacientes são fisicamente capazes de levar uma vida independente e sua deficiência é leve a moderada; estágio IV, doença gravemente incapacitante totalmente desenvolvida, o paciente ainda é capaz de andar e ficar de pé sem ajuda, mas está acentuadamente incapacitado; estágio V, confinamento à cama ou cadeira de rodas, a menos que seja auxiliado (HOEHN; YAHR, 1967)

2.2. Epidemiologia

Mundialmente, os principais causadores de incapacidade são os distúrbios neurológicos, e em comparação com outras doenças deste tipo a incidência de DP tem aumentado de forma mais rápida. Seguido do Alzheimer que é a mais prevalente, a DP é a segunda doença neurodegenerativa com maior número de casos no mundo, representando cerca de 2% de toda a população, em 2016 o número de diagnósticos de DP foi aproximadamente 2,4 vezes maior que em 1990 (BOVOLENTA; FELICIO, 2017; RAY DORSEY et al., 2018). Este fato pode estar relacionado ao envelhecimento populacional, o aumento da expectativa de vida, melhorias no diagnóstico e a maior compreensão da doença (ARMSTRONG; OKUN, 2020).

No território brasileiro, cerca de 3,3% da população acima dos 64 anos tem o diagnóstico de DP. Em 2016 o número de diagnósticos em pessoas com média de 70 anos foi de aproximadamente 128.836 casos, 8,5% para as pessoas entre 80 e 85 anos e 14,3% para os indivíduos acima dos 85 anos (BOVOLENTA; FELICIO, 2017; CAMPOS et al., 2015; MONTEIRO et al., 2014; SILVA; CARVALHO, 2019; SOUZA et al., 2011; TYSNES; STORSTEIN, 2017).

Em 2013, o Brasil teve um custo anual com serviços de saúde de R$ 131,5 bilhões, equivalente a 8% de seu PIB (Produto Interno Bruto) (BOVOLENTA; FELICIO, 2017). Este valor inclui consultas médicas regulares, medicamentos, exames complementares, hospitalizações e programas multiprofissionais de reabilitação. Desta forma, é essencial a utilização de estratégias que minimizem o desenvolvimento da DP na população para que desta maneira seja reduzido os gastos com o sistema de saúde e que priorizem a saúde do idoso (BOVOLENTA; FELICIO, 2017). A DP é a doença neurodegenerativa com maior custo para os serviços de saúde e esses pacientes são os que mais consomem estes serviços por ser uma doença que não tem cura e necessita de cuidados por toda a vida (BOVOLENTA; FELÍCIO, 2016; GUO et al., 2013).

2.3. Sinais e sintomas

Na DP estão presentes SMs, a exemplo da rigidez que é caracterizada pelo aumento do tônus muscular resultando numa maior resistência à movimentação passiva e, também, manifesta nos órgãos internos tornando-os mais lentos (DE SANT et al., 2008). O tremor de repouso que está presente em cerca de 75% das pessoas com DP e é um dos sintomas iniciais da doença, pode ser intensificado com a marcha e esforço mental em situações de tensão emocional (FABRICIA et al., 2011). Outro SM é a bradicinesia definida como a diminuição da velocidade da execução dos movimentos voluntários impactando na dificuldade para iniciar os movimentos (DE SANT et al., 2008). Além desses sintomas, as pessoas com DP têm também alterações posturais como flexão da maioria das articulações, ombros em rotação interna, flexão de tronco e anteriorização da cervical (DE SANT et al., 2008; FABRICIA et al., 2011).

Dentre os SNMs é observado que, aproximadamente, 45% das pessoas com DP têm depressão e estas condições têm um envolvimento complexo pela disfunção de vias do sistema límbico, e a ansiedade está associada à depressão na maior parte dos casos, podendo resultar numa ansiedade geral, ataques de pânico e fobia social (CHAUDHURI; SCHAPIRA, 2009). Disfunção cognitiva está presente em cerca de 80% dos pacientes quando estão nos estágios mais avançados, refletindo na memória, atenção, linguagem e visualização espacial (WILLIAMS-GRAY et al., 2007). Pessoas com DP podem ter também distúrbios do sono, que podem surgir como insônia, podendo ser no início ou na fase de manutenção do sono, ou na forma de síndrome das pernas inquietas ou até mesmo como um transtorno comportamental durante o sono REM (*rapid eye moviment sleep)* (CHAUDHURI; SCHAPIRA, 2009).

2.4. Dor na doença de Parkinson

A dor é um outro SNM presente na DP e é considerada com heterogênea e incapacitante (ANTONINI et al., 2018; BROEN et al., 2012; DEFAZIO et al., 2013; LUK et al., 2012). Já se passaram mais de 200 anos desde as primeiras descrições da DP, contudo, a dor continua a ser um sintoma subestimado e subdiagnosticado nesta doença (ANTONINI et al., 2018). A dor é relatada por cerca de 50 a 85% dos casos nesta população (BROEN et al., 2012; CURY et al., 2020; GREENBAUM et al., 2012; LUDWIG, 2008; MORENO et al., 2012) e aproximadamente 40% dos pacientes não relatam este sintoma aos seus neurologistas por acreditarem que não tem relação com a

DP (CHAUDHURI et al., 2010). O sintoma dor diminui a qualidade de vida destes pacientes e tem um maior impacto do que os SMs (CERRI; MUS; BLANDINI, 2019ª; QUITTENBAUM; GRAHN, 2004ª; SILVERDALE et al., 2018b). Além disso, ela interfere diretamente no desempenho das atividades de vida diária e laboral destes pacientes (ALLEN et al., 2016; DE MATTOS et al., 2019).

2.5. Métodos de caracterização da dor na doença de Parkinson

Os principais fatores para o subdiagnóstico e o subtratamento da dor em pessoas com DP são as dificuldades de definição e tratamento (ANTONINI et al., 2018). Diversas classificações já foram propostas a exemplo da forma dicotômica como nociceptiva ou neuropática, primária ou secundária (SNIDER et al., 1976; WASNER; DEUSCHL, 2012). Também foi sugerido a classificação de Ford que é baseada na etiologia da dor associada aos sintomas motores, ela é dividida em dor musculoesquelética, dor distônica, dor radicular/neuropática, dor central ou primária e acatisia (FORD, 2010).

Outra forma de diagnosticar este sintoma é através da *King's Parkinson Disease Pain Scale* (KPPS), recentemente validada no Brasil, que tem como objetivo identificar e graduar a dor desta população. Ela é composta por sete domínios que incluem quatorze itens, cada item pontuado de acordo com a severidade (0-3), multiplicado pela frequência (0-4), com um resultado parcial de 0 a 12, com um total possível de 0-168 pontos, sendo que quanto maior o escore, maior será o impacto da dor na vida deste paciente (CHAUDHURI et al., 2015; COIMBRA et al., 2021). Outros autores sugerem que a dor em pessoas com DP deve ser classificada de acordo com os conceitos da *International Association for the Study of Pain* (IASP) com base nos mecanismos da dor. Além destas formas de classificar, diversos são os instrumentos utilizados para caracterizar e dimensionar a dor, a exemplo do EVA (Escala Visual Analógica), END (Escala Numérica da Dor), BPI (*Brief Pain Inventory*), MPQ (*McGill Questionary*), dentre outros (CARLSSON, 1983; CLEELAND; RYAN, 1994; MELZACK, 1975; RAKEL et al., 2012).

A avaliação clínica juntamente com instrumentos apropriados para a caracterização da dor é fundamental para os estudos dos sintomas e tratamentos da DP. Sendo assim, o diagnóstico adequado e a classificação dos diferentes subtipos de dor serão essenciais para a prescrição do tratamento para os pacientes.

3. OBJETIVO

Caracterizar a dor em pessoas com doença de Parkinson e identificar os principais instrumentos para avaliação deste SNM.

4. MÉTODO

O protocolo definido para esta revisão sistemática aderiu às recomendações propostas pelo *The Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA) (PAGE et al., 2021). Este estudo foi submetido ao *International Prospective Register of Systematic Reviews* (PROSPERO), número de registro CRD42021243043. A pergunta desta revisão é "Quais as características relacionadas à dor em pessoas com doença de Parkinson?". Este estudo foi estruturado com a estratégia PECO: P – População de interesse: Doença de Parkinson; E – Exposição: Dor; C – Controle: Pessoas sem DP; O – Desfecho: Características da dor (BRASIL. MINISTÉRIO DA SAÚDE; DEPARTAMENTO DE CIÊNCIA E TECNOLOGIA., 2014).

4.1 Critérios de inclusão e exclusão

Foram incluídos estudos observacionais, do tipo transversal, longitudinal, caso-controle, coorte e que tinham como população estudada os indivíduos com DP, sem restrição de idioma ou data de publicação dos estudos. No entanto, foram excluídos os estudos que tiveram como público-alvo pessoas com parkinsonismo ou transtornos de Parkinson e que apresentaram alterações neurológicas relacionadas à COVID-19 e/ou SARS-CoV-2.

4.2 Estratégia de busca

Foram realizadas pesquisas em 9 bases de dados para encontrar estudos que atendam os critérios dessa revisão: Biblioteca Nacional de Medicina *(MEDLINE-PubMed), Scielo, Lilacs, Cochrane, PEDro, PsycINFO, SPORTDiscus, Web of Science (WOS)* e *Scopus*. Além destas, foi realizada a pesquisa na literatura cinzenta, onde foram selecionados os 100 primeiros artigos da busca realizada no *Google Scholar*, e a *Hand Search* que é a busca nas referências dos estudos incluídos para potenciais artigos a serem selecionados. A estratégia de busca utilizada foi a combinação dos termos utilizados como descritores "*Parkinson disease*" e "*Pain*" com o operador boleano "*AND*" em cada base de dados como está descrito na tabela 1. Não houve restrição de idioma e foram coletados todos os artigos publicados até o dia 18 de abril de 2022, data em que as pesquisas foram finalizadas.

Para as bases de dados PEDro, foram realizadas duas formas de busca após ser observada diferença em número e nos títulos dos artigos encontrados nas bases de

dados (“PEDro: Search,” [s.d.];) (ver detalhes na tabela 1). Alguns dos estudos selecionados não categorizaram no método qual o tipo de estudo observacional longitudinal foi realizado, sendo assim os avaliadores do presente estudo (EOM e MIOD) tomaram esta decisão de acordo com o desenho metodológico que cada um desses estudos.

Tabela 1 – Combinações dos descritores e filtros selecionados em cada base de dados utilizada.

Base	Descritores
COCHRANE	Parkinson disease AND pain
GOOGLE SCHOLAR	Parkinson disease AND pain
LILACS	Parkinson disease [words] AND pain [words]
PEDRO (search advanced)	Parkinson disease AND pain
PEDRO (search simple)	Parkinson disease AND pain
PSYCINFO	Parkinson disease AND pain
PUBMED	(“Parkinson disease” [Mesh]) AND “Pain” [Mesh]
SCIELO	(Parkinson disease) AND (pain)
SCOPUS	Parkinson disease AND pain (review, article)
SPORTDISCUS	Parkinson disease AND pain
WEB OF SCIENCE	Parkinson disease AND pain (review, article, data paper)

4.3 Extração dos dados

Todos os artigos encontrados foram avaliados sequencialmente quanto aos títulos, resumos e textos completos, por dois revisores (EOM e MIOD), de forma separada e independente, de acordo com os critérios de inclusão e exclusão do presente estudo. Os dados dos artigos selecionados foram registrados de forma padronizada pelos avaliadores em uma planilha do Excel®. Para os artigos em que houve conflito de opinião entre os avaliadores, foi decidido em consenso com a participação de um terceiro avaliador sênior (JMS). Para os estudos em que os dados estiveram inconclusivos ou incompletos, foi solicitado aos autores para que os mesmos enviassem os dados na íntegra com um prazo de resposta de 15 dias ou o artigo seria excluído da revisão.

Foram coletados os nomes dos autores, título, hipótese, objetivos, cálculo amostral, descrição e número de participantes, variáveis investigadas, instrumentos utilizados e os seguintes desfechos: mecanismo da dor (neuropática, nociceptiva, nociplástica, mista e não identificada); local da dor; tempo de dor; intensidade de dor;

fatores de alívio e de exacerbação; cronologia da dor (dor aguda ou crônica); origem da dor (primária ou secundária); terminologia do tipo de mecanismo da dor relatada nos critérios de inclusão; terminologia do tipo de mecanismo da dor apresentada nos resultados diante dos dados encontrados.

4.4 Avaliação do risco de viés

A ferramenta utilizada para avaliação da qualidade metodológica dos artigos incluídos foi a publicada pelo *National Heart, Lung and Blood Institute* (NHLBI) ("Study Quality Assessment Tools | NHLBI, NIH", [s.d.]), anexo 1. A avaliação do risco de viés foi realizada de forma independente pelos dois avaliadores. Para os estudos do tipo coorte ou transversais, esta ferramenta consiste em 14 itens - cada um dos quais pode ser marcado como Sim (Y), Não (N) e Não Reportado (NR) ou Não Aplicável (NA) ou Não Pode Determinar (CD). Já para os estudos do tipo caso-controle, consiste em 12 itens - cada um dos quais pode ser marcado da mesma forma já citada. Para a representação da avaliação do risco de viés dos estudos, os avaliadores (EOM e MIOD) utilizaram a forma de tabela e a colorimetria para descrever as marcações de cada item e dessa forma seja possível ter uma melhor visualização, sendo assim, foi aplicada a cor verde para Sim (Y), a cor vermelha para Não (N) e, por fim, a cor amarela para Não Reportado (NR) ou Não Aplicável (NA) ou Não Pode Determinar (CD). Também foi utilizado como ponto de corte 50% do numero de falhas metódologicas de acordo com cada ferramenta, ou seja, 7 falhas para os 14 itens para os estudos do tipo coorte e transversal e 6 para os 12 itens para os estudos do tipo cas-controle.

Os 14 itens para a avaliação dos estudos do tipo coorte ou transversais são as seguintes perguntas: 1. A questão de pesquisa ou objetivo neste artigo foi claramente declarado; 2. A população do estudo foi claramente especificada e definida; 3. A taxa de participação das pessoas elegíveis foi de pelo menos 50%; 4. Todos os indivíduos foram selecionados ou recrutados da mesma população ou de populações semelhantes (incluindo o mesmo período de tempo). Os critérios de inclusão e exclusão por estar no estudo foram pré-especificados e aplicados uniformemente a todos os participantes; 5. Foi fornecida uma justificativa do tamanho da amostra, descrição do poder ou estimativas de variação e efeito; 6. Para as análises deste artigo, a(s) exposição(ões) de interesse foi(m) medida(s) antes do(s) resultado(s) serem medidos; 7. O prazo foi suficiente para que se pudesse razoavelmente esperar ver uma associação entre exposição e desfecho, caso existisse; 8. Para exposições que podem variar em quantidade ou nível, o estudo

examinou diferentes níveis de exposição em relação ao resultado (por exemplo, categorias de exposição ou exposição medida como variável contínua); 9. As medidas de exposição (variáveis independentes) foram claramente definidas, válidas, confiáveis e implementadas de forma consistente em todos os participantes do estudo; 10. A(s) exposição(ões) foi(m) avaliada(s) mais de uma vez ao longo do tempo; 11. As medidas de resultado (variáveis dependentes) foram claramente definidas, válidas, confiáveis e implementadas de forma consistente em todos os participantes do estudo; 12. Os avaliadores de resultados estavam cegos para o status de exposição dos participantes; 13. A perda de seguimento após a linha de base foi de 20% ou menos; 14. As principais variáveis de confusão potenciais foram medidas e ajustadas estatisticamente para seu impacto na relação entre exposição(ões) e desfecho(s) ("Study Quality Assessment Tools | NHLBI, NIH", [s.d.]).

Para a avaliação dos estudos do tipo caso-controle são usados os 12 itens formados pelos questionamentos: 1. A questão de pesquisa ou objetivo neste artigo foi claramente declarado e apropriado; 2. A população do estudo foi claramente especificada e definida; 3. Os autores incluíram uma justificativa para o tamanho da amostra; 4. Os controles foram selecionados ou recrutados da mesma população ou similar que deu origem aos casos (incluindo o mesmo período de tempo); 5. As definições, critérios de inclusão e exclusão, algoritmos ou processos usados para identificar ou selecionar casos e controles foram válidos, confiáveis e implementados de forma consistente em todos os participantes do estudo; 6. Os casos foram claramente definidos e diferenciados dos controles; 7. Se menos de 100 por cento dos casos e/ou controles elegíveis foram selecionados para o estudo, os casos e/ou controles foram selecionados aleatoriamente dentre os elegíveis; 8. Houve uso de controles simultâneos; 9. Os investigadores foram capazes de confirmar que a exposição/risco ocorreu antes do desenvolvimento da condição ou evento que definiu um participante como um caso; 10. As medidas de exposição/risco foram claramente definidas, válidas, confiáveis e implementadas de forma consistente (incluindo o mesmo período de tempo) em todos os participantes do estudo; 11. Os avaliadores de exposição/risco estavam cegos para o status de caso ou controle dos participantes; 12. As principais variáveis de confusão potenciais foram medidas e ajustadas estatisticamente nas análises. Se o emparelhamento foi usado, os investigadores consideraram o emparelhamento durante a análise do estudo ("Study Quality Assessment Tools | NHLBI, NIH", [s.d.]).

4.5 Análise de dados

Após a extração dos dados e a análise do risco de viés, foi realizada a análise quantitativa, por meio da geração de metadados dos estudos incluídos que apresentaram instrumentos de mensuração de desfecho semelhante (dor). Foram analisados os resultados dos instrumentos BPI (severidade e intensidade), EVA e KPPS. A heterogeneidade dos estudos fora verificada por meio do teste de mesmo nome (I2) e um valor de $p \leq 0,05$ foi considerado estatisticamente significativo. Ademais, fora aplicado o efeito aleatório devido à alta heterogeneidade apresentada pelas características dos estudos. Exceto quando da ocorrência de *overlap,* como constatado nas análises de sub-grupo referentes ao BPI, neste caso foi aplicado o efeito fixo.

As meta-análises foram realizadas por meio do software Cochrane collaboration's Review Manager versão 5.3.5, dispositivo oficial do Informatics & Knowledge Management Department Cochrane.

5. RESULTADOS

De acordo com a estratégia de busca descrita, foram encontrados 14.197 artigos, sendo excluídos 11.652 com base nos critérios de inclusão e 2.269 duplicatas. Por fim, foram selecionados 94 artigos publicados até 18 de abril de 2022, sendo 66 estudos do tipo coorte e transversal, e 28 estudos do tipo caso-controle. Os detalhes da seleção dos artigos estão descritos na figura 1. Na tabela 2 estão caracterizados todos os artigos incluídos.

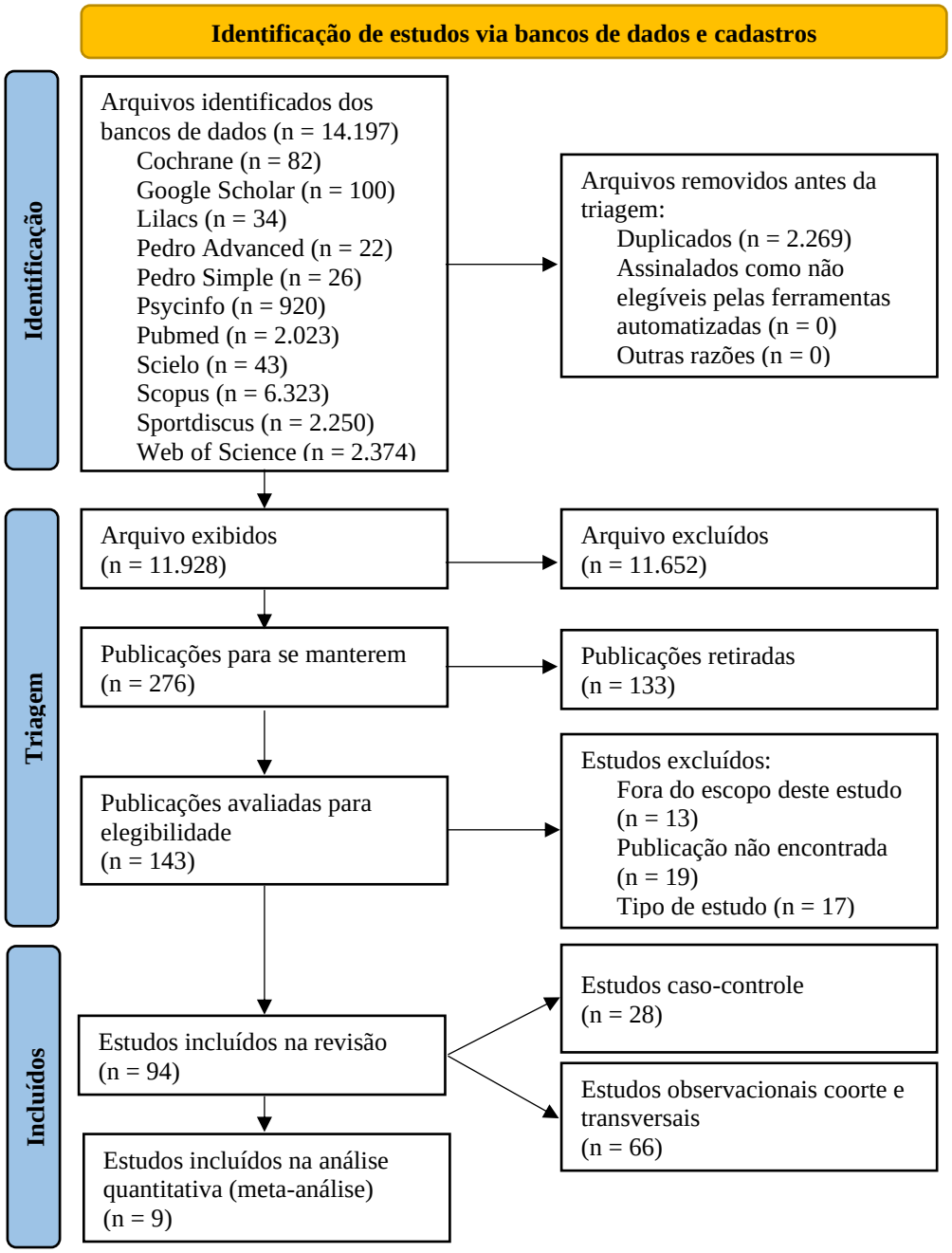

Figura 1: Fluxograma da seleção dos artigos.

Tabela 2 – Detalhamento das principais informações dos artigos incluídos

Autor, data	Tipo do Estudo	Participantes	Variáveis	Instrumentos de avaliação	Principais resultados
Indo, et al., 1983	Observacional transversal	71 pessoas com DP	Características das cefaleias †	Questionário †	Cefaleia foi observada em 8 de 24 pacientes do sexo masculino e em 17 de 47 do sexo feminino (35,2% ao todo). O número total de casos de cefaleia classificados por local (um caso pode aparecer em mais de um local) foi: região nucal (n=10), regiões temporal e occipital (n=8, cada), região frontal (n=5) e cabeça inteira (n=1). Quanto à natureza da cefaleia, a dor impertinente foi mais frequente (16 dos 25 casos de cefaleia), seguida de oito casos de dor pulsátil. Variações diurnas de cefaleia foram observadas em 12 casos (48%), mas foram leves em todos, exceto em um caso.
Starkstein et al., 1991	Observacional transversal*	79 pessoas com DP	Depressão Diagnóstico de distúrbios mentais Dor Exame neurológico Função cognitiva Sono	Escala de Depressão de Hamilton DSM-III PSE Questionário de dor Questionário de McGill NWDE MMSE SQ	Uma análise de regressão *stepwise* foi realizada, com o Questionário de McGill ou o SQ como variáveis dependentes, e idade, duração da doença, dosagem de levodopa, tremor, rigidez, amnésia, MMSE, NWDS e PSE como variáveis independentes. Os pacientes do grupo MA apresentaram pontuações SQ significativamente mais altas (ou seja, mais distúrbios do sono) do que o grupo NO. As pontuações do

					MPQ também foram significativamente mais altas (ou seja, dor mais intensa) em pacientes com MA em comparação com pacientes com MI e NO. A análise MPQ mostrou uma frequência semelhante de dor nos três grupos.
Djaldetti et al., 2004	Observacional caso-controle* 28 controles saudáveis	36 pessoas com DP	Intensidade de dor Limiar sensitivo mecânico Sensibilidade térmica Sensibilidade a dor	EVA Filamentos de von Frey *Peltierbased contact*† Limiares de dor térmico†	Os limiares mecânico e sensibilidade térmica não diferiram em ambos os grupos de pacientes e controles, nem entre os lados. O limiar de dor térmico foi menor em pacientes com DP que sentiram dor em comparação com aqueles que não tiveram e aqueles que sentiram dor no lado mais afetado. Em pacientes com flutuações não houve diferenças laterais em sensibilidade térmica e limiar de dor térmico ou entre os períodos "on" e "off".
Quittenbaum & Grahn, 2004	Observacional caso-controle* Controlado, Descritivo Transversal 95 controles saudáveis	57 pessoas com DP	Intensidade de dor Local de dor Qualidade de vida	EVA Desenho da dor SF-36	Problemas de dor são comuns em pacientes com DP, mas também em grande parte na população saudável. A QVRS foi reduzida para os pacientes com DP em todas as escalas do SF-36 e consequentemente também na dimensão dor.
Giuffrida et al., 2005	Observacional retrospectivo	388 pessoas com DP	Dor† Topografia da dor	Questionário† Autorrelato	Entre esses pacientes com doença de Parkinson responsiva à dopamina diagnosticada clinicamente, 269 (67%) apresentaram síndromes sensoriais ou dolorosas. Entre eles, 94% apresen-

tavam dores musculares: rigidez (85%), cãibras, pseudocãibras, espasmos (3%) ou mialgias diversas (7%); 51% apresentavam dor osteoligamentar "reumatológica", articular (23%), periarticular (3%) ou espinhal (31%), mas síndromes dolorosas neurogênicas menos definidas e localizadas foram menos frequentes (8%), como parestesia (6%), disestesia (<1%), sensação de queimação (2%), coceira (<1%), desconforto mal definido (6%) ou sensação de peso (1%), com segmento (86%), axial (54%), radicular ou pseudorradicular (14%), distal (4%) ou menos frequentemente distribuição anorretal ou visceral. Pernas inquietas ou acatiasia foram ocasionais (10%). Dores de cabeça e dor facial foram menos frequentes (1%), não foi encontrado dor fantasma. Mais de um quarto estavam presentes no início da doença, apenas (3%) deles resolvidos durante o desenvolvimento da doença. Cerca de um terço estava claramente ligado a flutuações motoras, a maioria ocorrendo na fase *off* (34%). Não foi encontrado correlação com idade, sexo, duração ou estágio da doença, dose

					equivalente de L-dopa, depressão, insônia ou disfunção autonômica.
Lee et al., 2006	Observacional transversal	123 pessoas com DP	Depressão Dor† Estágio da doença Função Cognitiva	BDI PACA BPI EVA Autorrelato Hoehn-Yahr MMSE	Os pacientes relataram 285 locais de dor (mediana de 2 por paciente) e 22,8% apresentaram 4 ou mais dores. A dor foi relatada como um problema em 85% e relacionada à DPI em 62,6% dos pacientes, não relacionada à DPI em 64,2%, indiretamente relacionada à DPI em 8,1%, relacionada a múltiplas causas em 4,1% e relacionada ao tratamento em 0,8%. A dor não relacionada à DPI foi mais comum, mais constante e mais intensa do que a dor relacionada à DPI. No geral, o uso de analgésicos foi baixo.
Tinazzi et al., 2006	Observacional transversal	117 pessoas com DP	Depressão Duração e localização da dor Intensidade da dor SMs	BDI Autorrelato EVA UPDRS	A dor foi descrita por 47 pacientes (40%) e pode ser classificada em dor distônica (n:19) e não distônica (n:16); em 12 pacientes ambos os tipos coexistiram. Modelos de regressão logística de variáveis explicativas múltiplas indicaram associação significativa de dor com complicações motoras. Não foi encontrada associação entre dor, distônica ou não distônica, e as demais variáveis investigadas, incluindo condições médicas sabida-mente associadas à dor na população geral. Houve uma correlação

					significativa entre a gravidade da dor (medida em uma Escala Visual Analógica) e a gravidade das complicações motoras (UPDRS parte IV).
Broetz et al., 2007	Observacional caso-controle*	101 pessoas com DP 132 pessoas pós-AVC ou com tumor cerebral	Dor radicular	Questionário estruturado†	A prevalência de dor nas costas foi de 74% em pacientes com DP (n=101) quando comparada com 27% em pacientes controle (n=132), mas não se correlacionou com a gravidade ou duração da doença. A intensidade média da dor nas costas (EVA de 0-10) foi de 4,3 para pacientes com DP e 1,3 para controles. Ambos os tipos de dor nas costas (radicular e não radicular) foram mais frequentes, e a dor nas costas causou mais comprometimento em pacientes com DP. No entanto, vale ressaltar que os pacientes com DP neste estudo não receberam mais medicação para dor do que os pacientes controle.
Defazio et al., 2008	Observacional caso-controle	402 pessoas com DP 317 controles saudáveis	Cronologia e local da dor Depressão Estadiamento da DP Intensidade de dor SMs e SNMs	Autorrelato BDI Hoehn-Yahr EVA UPDRS	A frequência geral de dor foi significativamente maior em pacientes com DP do que em controles (281 [69,9%] vs 199 [62,8%]), principal-mente porque o grupo controle saudável não apresentava dor distônica. Por outro lado, a frequência de dor não distônica foi semelhante entre pacientes com DP e controles (267

					[66,4%] vs 199 [62,8%]). No entanto, observamos uma associação significativa entre DP e dor não distônica, começando após o início dos sintomas parkinsonianos. Cólicas e dor neuropática central foram mais frequentes entre os pacientes com DP do que os controles. Cerca de um quarto dos pacientes que sentiram dor relataram o início da dor antes de iniciar a terapia antiparkinsoniana.
Silva, et al., 2008	Observacional transversal* prospectivo	50 pessoas com DP	Dependência de um cuidador Dor† Gravidade da doença SMs	*Schwab and England's scale* Questionário † END Hoehn-Yahr UPDRS	Vinte e oito pacientes relataram dor; comparando o grupo com dor e o grupo sem dor, não houve diferenças relacionadas ao início da doença e aos sintomas motores da DP. No entanto, muitos pacientes relataram melhora da dor quando a terapia antiparkinsoniana foi iniciada ou ajustada.
Beiske et al., 2009	Observacional transversal*	176 pessoas com DP	Características da DP, dados demográficos e sensibilidade somática Função cognitiva Gravidade da doença Dor†	Questionário MMSE Hoehn-Yahr BPI [itens 3,4,5 e 6] Escala Likert de 10 pontos	A dor foi relatada por 146 (83%) pacientes. Em comparação com a população geral, os pacientes com doença de Parkinson experimentaram significativamente mais dor, conforme medido pela Escala de Dor Corporal do SF-36. A média de dor nas últimas 24 h medida pelo BPI foi de 2,85. Cinquenta e três por cento dos pacientes relataram um, 24% relataram dois e 5% relataram três tipos de dor. Dor musculoesque-

				Domínio dor do SF-36 Questionário estruturado sobre dor	lética foi relatada por 70%, dor distônica por 40%, dor neuropática radicular por 20% e dor neuropática central por 10%. Trinta e quatro por cento estavam em medicação analgésica. A dor não foi associada à idade, duração da doença ou gravidade da doença; o sexo feminino foi o único preditor significativo de dor. A dor é frequente e incapacitante, independente de variáveis demográficas e clínicas, exceto sexo feminino, e é significativa-mente mais comum em pacientes com Parkinson em comparação com a população geral. Uma minoria dos pacientes com doença de Parkinson com dor recebeu medicação analgésica.
Ehrt et al., 2009	Observacional caso-controle	227 pessoas com DP 100 controles saudáveis	Depressão Dor† Função cognitiva SMs	MADRS BDI NHP MMSE UPDRS	Sessenta e sete por cento dos pacientes com DP sofriam de dor, em comparação com 39% do grupo controle. Indivíduos com DP com dor tiveram pontuações mais altas no MADRS e BDI, e eram mais propensos a ter depressão do que pacientes com DP sem dor. Nas análises multivariadas, a presença de dor foi significativamente associada aos escores de depressão, mesmo após ajuste para variáveis demográficas e clínicas.

Polidorio et al., 2009	Observacional transversal	15 pacientes com DP 15 controles saudáveis	Impacto da dor na DP	Questionário de McGill	Dor foi relatada em 53% de GI (n = 8) e 47% de GII (n=7). Um pequeno aumento nas respostas negativas sobre vida social e no cotidiano foi observado em GI. Essa impressão não atingiu diferença estatisticamente significativa em nenhum dos itens do Questionário de McGill.
Roh et al., 2009	Observacional transversal*	82 pessoas com DP	Depressão Gravidade da DP Intensidade de dor Qualidade de vida Queixas somáticas/ ansiedade SMs	Inventário de Depressão Zung Hoehn-Yahr EVA SF-36 Questionário de Percepção Somática Modificado UPDRS	O grupo DP com dor teve pontuações no UPDRS parte III mais altas, pontuações no SF-36 mais baixas, pontuações no Questionário de Percepção Somática Modificado mais altas do que o grupo DP sem dor. A presença de dor, estágio de Hoehn e Yahr elevado, idade avançada e percepção somática foram os fatores que influenciaram negativamente o componente físico da SF-36. Depressão e percepção somática foram os fatores preditivos mais importantes para o componente mental da SF-36. Depressão e habilidades motoras deficientes parkinsonianas foram os principais fatores que contribuíram para a dor.
McNamara et al., 2010	Observacional caso-controle	23 pessoas com DP	SMs e Informações de medicação Humor	Questionário estruturado DASS	Ambos os grupos de DP relataram maiores pontuações de intensidade de dor atual, maior intensidade de dor em

		11 controles saudáveis	Intensidade de dor Queixas subjetivas de dor	EVA Questionário de McGill Questionário de Dor	geral do que os participantes do controle. Houve uma associação significativa entre o humor e todas as classificações de dor de McGill nos pacientes com início da DP do lado esquerdo, com aqueles que relataram mais sintomas de humor classificação mais alta em todas as escalas de dor. Essa associação não foi encontrada nos pacientes com início da DP do lado direito.
Müller, et al., 2011	Observacional transversal*	4086 pessoas com DP	Intensidade de dor	EQ-5D (domínio dor)	Os pacientes com DP foram divididos em três grupos de acordo com sua pontuação total EQ-5D. Ocorreu um comprometimento do estado de saúde em relação ao aumento das síndromes dolorosas em pacientes com DP. Houve um aumento significativo nos escores EVA em relação à participação no grupo EQ-5D. Pacientes do sexo feminino relataram maior intensidade de dor e receberam mais frequente-mente um tratamento medicamentoso para a dor do que os pacientes do sexo masculino. Associações significativas foram encontradas entre os escores EVA e EQ-5D, e os coeficientes de correlação foram maiores nos homens do que nas mulheres.

Mylius et al., 2011	Observacional caso-controle*	29 pessoas com DP 27 controles saudáveis	Depressão Função cognitiva Gravidade da doença Limiar elétrico de dor Latência térmica de dor Gravidade de dor Reflexo de flexão noceptiva SMs	Escala Geriátrica de Depressão MMSE Hoenh-Yahr NFR Avaliação dos limiares de dor elétrica *Peltierbased contact* Classificação de Ford Neurografia sural UPQRS	Os dados forneceram evidências de que a nocicepção espinhal e a sensibilidade à dor são preservadas durante a fase inicial da doença de Parkinson. Após aumento da nocicepção espinhal, a sensibilidade térmica e elétrica experimental à dor foi aumentada durante o curso da DP, enquanto a nocicepção espinhal aumentou ainda mais. O aumento da sensibilidade à dor experimental foi observado em pacientes que apresentavam dor relacionada à doença de Parkinson.
Skogar et al., 2012	Observacional transversal*	45 pessoas com DP	Distúrbios do sono Dor Qualidade de vida	PDSS Diário de dor Autorrelato EVA *Pain Evaluation Analysis* Questionário Pain-O-Meter SF-36	Em um terço dos participantes, a dor precedeu o diagnóstico de DP. A pontuação mediana da dor medida com uma escala visual analógica foi de 6,6 e 5,9 (para mulheres e homens, respectivamente) na semana anterior ao estudo. Em quase metade dos participantes, a dor esteve presente durante todas as horas de vigília. Significativamente mais mulheres descreveram sua dor como problema-tica, enquanto mais homens descreve-ram sua dor como irritante. Sensações de dormência e sensação de rastejar à noite foram fortemente associadas com os escores máximos da escala analógica visual. A

					polifarmácia era comum; 89% usavam medicação para ansiedade/insônia e 18% usavam antidepressivos. Apenas um terço dos pacientes que relataram alívio da dor com analgésicos os tinham prescrito em suas listas de medicamentos. O sono foi caracterizado por despertares frequentes. Urgência urinária e pernas inquietas foram frequentemente relatados como incômodos. Os pacientes classificaram a qualidade de vida como significativamente pior em todos os itens em comparação com uma população de referência saudável pareada por idade e sexo.
Rana et al., 2013[1]	Observacional transversal	121 pessoas com DP	Intensidade de dor Características da dor física	EVA Questionários derivado do BPI	A dor foi relatada por 80 (66%) pacientes com média de idade ao diagnóstico da DP de 67,26±11,43 anos. Os tipos clínicos de dor mais comuns experimentados pelos pacientes foram dor distônica (48%), parestesia/dor neuropática (36%) e dor musculoesquelética (28%). Os pacien-tes com DP descreveram sua experiência física de dor como dor (46%), sensação de tensão (18%), dor aguda (12%), dor profunda (12%) e dor maçante (11%). Pacientes com DP afetando o lado direito do corpo tiveram quatro vezes mais chances de relatar dor no lado

					direito do corpo; entretanto, tal relação não foi encontrada para o lado esquerdo do corpo. Uma pontuação mais alta na escala UPDRS-III e maior duração da DP reduziram a probabilidade de os pacientes relatarem dor incômoda. A presença de parestesia/dor neuropática mostrou diminuir a probabilidade de os pacientes relatarem dor aguda. Não foram encontradas relações significativas entre a magnitude da dor e sexo, idade no diagnóstico da DP, duração da DP, pontuação UPDRS-III ou estágio Hoehn e Yahr da DP. Embora 40% dos pacientes com DP sentissem que a medicação tinha um efeito (direto) em sua dor, nenhuma relação foi encontrada entre a gravidade da dor e a medicação para DP.
Rana et al., 2013[2]	Observacional caso-controle	127 pessoas com DP 127 controles saudáveis	Dor† Síndrome das Pernas Inquietas SMs	BPI Escala de classificação de gravidade síndrome das pernas inquietas UPDRS	Os resultados mostraram que 21,3% dos pacientes com DP apresentavam SPI, em comparação com apenas 4,7% no grupo controle, representando uma diferença altamente significativa. A frequência de relato de dor também foi significativamente maior entre os pacientes com DP com SPI, mas não no grupo controle. No entanto, a diferença média na gravidade média da dor não foi significativamente diferente entre o

					DP com RLS e o não PD com RLS, nem o nível de dor e a gravidade foram significativamente correlacionados com a gravidade dos pacientes com início da DP do lado direito para ambos os grupos.
Coriolano et al., 2014	Observacional transversal	24 pessoas com DP	Características da dor Função cognitiva Gravidade da DP SMs	Questionário de McGill MMSE Hoehn-Yahr UPDRS	A região específica do corpo com dor mais frequente foi coluna lombar (50%). As regiões categorizadas com maior percentual de queixas foram: tronco (66,7%); membros superiores (37,5%) e inferiores (37,5%). A maioria dos pacientes referiu dor em apenas uma região do corpo, independentemente de se analisar as regiões específicas ou categorizadas (37,5%). Não houve diferença significativa na pontuação proporcional atingida por cada componente da pontuação do questionário McGill. Pacientes com DP do grupo rígido acinético apresentaram maior número de regiões do corpo com dor. A comparação entre as pontuações dos índices de McGill, segundo o sintoma predominante e segundo o estágio da DP (Hoehn-Yahr) não apresentou diferença significativa.
Rana et al., 2014	Observacional caso-controle	127 pessoas com DP	Dor†	BPI Questionário	Pacientes com DP tiveram menor chance de sentir dor em ambos os

		127 controles saudáveis			braços, maior probabilidade de demonstrar dor em ambas as pernas e maior dificuldade em localizar a dor. Não houve relação entre duração da dor ou artrite e dor na DP. A probabilidade de sentir dor persistente, mas não outras formas, foi muito mais fortemente associada a pacientes com DP do que controles normais. Quando todos os outros tipos de dor foram controlados, a dor na DP está mais provavelmente associada à dor acatésica.
Paul et al., 2014	Observacional coorte	104 pessoas com DP	Gravidade da DP Intensidade de dor SMs Tipo de dor	Hoehn-Yahr EVA UPDRS Classificação de Ford	54,8% dos pacientes com DP sentem dor. A presença de sintomas sensoriais foi significativamente associada ao grupo com dor (42,1%) do que o grupo sem dor (21%). A dor foi mais pronunciada no lado com sintomas motores predominantes (72%) e em 68,4% a dor dos pacientes respondeu ao tratamento dopaminérgico. A dor musculoesquelética (82,5%) foi o tipo mais comum e os membros inferiores foram o local mais comum de dor (43,2%).
Mao et al., 2015	Observacional caso-controle*	142 pessoas com DP 80 controles saudáveis	Depressão Dor† Função cognitiva	HAND EVA Classificação de Ford MoCA Hoenh-Yahr	A incidência de dor foi de 47,9% em pacientes com DP, a maioria com níveis moderados de dor. Pacientes com dor apresentaram escores HRSD, UPDRS, Hoenh-Yahr e NMSQT mais

			Gravidade da doença SMs SNs	UPDRS NMSQT	altos e escores MoCA mais baixos em comparação aos pacientes sem dor. Os escores HRSD e NMSQT estavam intimamente relacionados com a dor.
Ohara et al., 2015	Observacional transversal*	186 pessoas com DP	Depressão Dor† Gravidade da doença Limiar elétrico de dor	BDI Questionário de McGill Hoenh-Yahr Pain Vision®	Um total de 186 pacientes completaram os questionários. A média de idade foi de 74±9,3 anos e a média do estágio Hoenh-Yahr foi de 2,8±0,8. Sessenta e nove por cento dos pacientes relataram sintomas álgicos de diversas naturezas. Os escores do BDI foram significativamente maiores no grupo de dor, apesar da ausência de diferenças estatisticamente significativas na idade média, estágio de Hoenh-Yahr e duração da doença. Apenas os pacientes com DP de estágio leve revelaram diferença significativa dos escores do BDI entre aqueles com dor e sem dor.
Priebe et al., 2015	Observacional caso-controle	23 pessoas com DP 23 controles saudáveis	Autoavaliação da dor Expressões faciais de dor Função cognitiva Sensibilidade à dor por calor SMs SNMs	Autorrelato FACS MMSE Limiar de dor pelo calor Somação temporal de dor por calor UPDRS NMSQT	Encontramos redução da atividade facial geral em resposta à dor em pacientes com DP no *Off*, que foi menos pronunciada no *On*. Especialmente o estreitamento ocular altamente relevante para a dor ocorreu com menos frequência em pacientes com DP do que em controles em ambas as fases, enquanto frequências de outros movimentos relevantes para a dor, como elevação do lábio superior (no *On*) e

					contração das sobrancelhas (em ambas as fases), não diferiu entre os grupos. Além disso, a abertura da boca (que muitas vezes não é considerada relevante para a dor) foi o movimento mais frequentemente exibido em pacientes com DP, enquanto o estreitamento dos olhos foi o movimento mais frequente nos controles. Não apenas mudanças quantitativas gerais no grau de expressividade da dor facial ocorreram em pacientes com DP, mas também mudanças qualitativas foram encontradas.
Tekin, 2015	Observacional retrospectivo	128 pessoas com DP 116 controles (cônjuges ou cuidadores dos participantes)	Dor em membro lesionado	Questionário estruturado	Sessenta e dois indivíduos relataram lesões nos membros antes do início dos sintomas de DP, 30 com e 32 sem dor crônica (ou seja, ≥ 2 meses). Não houve associação entre lesão e lado de início da DP em geral. Em indivíduos com dor crônica associada a lesões nos membros, entretanto, o lado das lesões foi associado ao lado do início dos sintomas da DP.
Valkovic et al., 2015	Observacional transversal*	100 pessoas com DP	Depressão Dor† Dor neuropática Gravidade da doença Qualidade de vida	BDI BPI LANSS Hoehn-Yahr	Um total de 76% dos pacientes apresentaram dor. Os seguintes tipos de dor estavam presentes: dor musculoesquelética respondeu por 41% do total de dores, dor distônica por 17%, dor neuropática central por 22%, dor

				PDQ-8	radicular por 27% e outras dores (lombalgia não radicular, artrítica, e dor visceral) representaram 24%. Um tipo de dor afetou 29% de todos os indivíduos, dois tipos 35%, três tipos 10% e quatro tipos de dor foram relatados por 2%. Todos os tipos de dor foram mais prevalentes em indivíduos com DP em estágio avançado do que em indivíduos com DP em estágio inicial, exceto para dor artrítica (subclassificada em "outras dores"). A frequência e intensidade da dor real, média e pior experimentada foram significativamente mais graves em indivíduos em estágio avançado. Indivíduos com DP com dor geral e em estágios avançados eram mais deprimidos e tinham pior QV. A depressão correlacionou-se com a pior dor nas últimas 24 horas e com a periodicidade da dor (o pior escore de depressão em pacientes com dor constante). A QV correlacionou-se com a média de dor nos últimos 7 dias.
Allen et al., 2016	Observacional transversal*	231 pessoas com DP	Dor interferindo no trabalho Frequência de dor	Escala de dor de 5 pontos Item 5 do SF-12v2 Soma dos itens 37, 38 e 39 do PDQ-39	A dor foi relatada por 187 (81%) participantes, com 91 (39%) relatando dor de gravidade moderada ou pior. A dor interferiu de alguma forma no trabalho em 158 (68%) participantes.

			Gravidade da doença Intensidade de dor	UPDRS Escala de dor de 6 pontos Item 21 do SF-36	Após o ajuste para idade e sexo, o aumento da rigidez foi associado a maior frequência de dor e mais dor que interferiu no trabalho. O tremor não foi associado a nenhuma medida de dor e deficiências motoras não foram associadas à gravidade da dor.
Gundogdu et al., 2016	Observacional caso-controle	112 pessoas com DP 120 controles saudáveis	Gravidade da DP Intensidade de dor Local da dor SMs	Hoehn-Yahr EVA Exame físico UPDRS	112 pacientes com DP e 120 controles pareados por idade e sexo foram entrevistados por um especialista em reabilitação sobre seus problemas musculoesqueléticos. A prevalência de dor musculoesquelética foi significativamente maior no grupo DP do que no grupo controle. Os locais do corpo comumente envolvidos foram a região lombar (46,4%), joelho (21,4%) e ombro (21,4%) no grupo DP, e região lombar (26,7%), joelho (20,0%) e tornozelo (11,7%) no grupo controle. A região lombar e o ombro foram mais frequentemente observados no grupo DP do que no grupo controle. Além disso, a frequência de camptocormia, síndrome de Pisa, deformidades estriadas da mão e do pé variou de 2,2 a 5,4% em pacientes com DP. A análise de regressão logística multivariada revelou que a presença de dor musculoesquelética foi associada ao

					sexo feminino, idade mais avançada e maior pontuação total UPDRS II no grupo DP, independente do estágio de Hoehn-Yahr, duração da doença e medicação.
Kubo et al., 2016	Observacional caso-controle multicêntrico	324 pessoas com DP 308 controles saudáveis	Gravidade da DP Intensidade de dor Local da dor SMs	Hoehn-Yahr Item 7 do SF-36v2 Ilustração do corpo UPDRS	A prevalência de dor no grupo DP foi de 78,6%, significativamente maior do que nos controles (49,0%), assim como sua gravidade. Não houve correlação entre o escore do SF-36v2 e os escores motores, como a UPDRS ou os escores de Hoehn-Yahr. A distribuição da dor foi semelhante entre os grupos, predominantemente na região lombar, seguida pela região glútea, pernas, coxas, região posterior do pescoço e ombros.
Lin et al., 2016	Observacional caso-controle	200 pessoas com DP 200 controles saudáveis	Ansiedade Depressão Dor neuropática Estado de dor física Função Cognitiva Gravidade da DP Intensidade de dor SMs	Escala de Ansiedade de Hamilton Escala de Depressão de Hamilton LANSS Domínio dor do SF-36 MMSE Hoehn-Yahr BPI UPDRS	Dos 200 pacientes com DP, a dor foi queixada por 106 pacientes (53%). De acordo com a Escala de Dor Corporal SF-36, a morbidade da dor em pacientes com DP foi significativa-mente maior do que no grupo controle. A dor média nas últimas 24 h medida pelo BPI foi de 2,67. Cerca de 76% dos pacientes com DP apresentavam um tipo de dor, 21,7% apresentavam dois tipos de dor e 1,9% apresentavam três tipos de dor. Além disso, 69,8% desses pacientes apresentavam dor musculoes-

					quelética, 4,7% com dor distônica, 22,6% com dor neuropática radicular, 20,8% com dor neuropática central e 9,4% com dor acatisia. A idade de início e a depressão foram os preditores mais significativos de dor em pacientes com DP. No entanto, não houve associação significativa entre dor e sexo, idade, duração da doença ou gravidade da doença. Apenas 5,7% dos pacientes com DP com dor receberam tratamento neste estudo.
Polli et al., 2016	Observacional caso-controle	40 pessoas com DP 15 controles saudáveis	Ansiedade Características da dor Depressão Função cognitiva Gravidade da DP SMs	Inventário de ansiedade de traço de estado KPPS EVA LANSS RMF BDI-II MMSE Hoehn-Yahr UPDRS	O grupo com DP e dor persistente apresentou adelgaçamento significativo no polo temporal bilateral, córtex orbito frontal medial esquerdo, áreas parietais superior e inferior esquerda bilateral, pars orbicular e córtex frontal superior direito, cingulado posterior e pré-central. Não houve diferenças significativas de volume subcortical e substância branca entre os subgrupos de DP. A RM funcional mostrou uma diminuição da atividade cerebral no orbital inferior frontal esquerdo em pacientes com DP com dor persistente, com maior atividade bilateral no cerebelo e nas áreas temporais inferiores direitas. Apenas pacientes com DP com dor persistente apresentaram

					desconexão accumbens-hipocampo sem substância branca e alterações subcorticais.
Rana et al., 2016[1]	Observacional caso-controle	123 pessoas com DP 123 controles saudáveis	Ansiedade Depressão Intensidade de dor Interferência da dor Incapacidade Prevalência da síndrome das pernas inquietas	HADS BPI Índice de Incapacidade de Dor Critérios diagnósticos da síndrome das pernas inquietas	Os pacientes com DP apresentaram significativamente maior gravidade da ansiedade, gravidade da depressão, gravidade da dor, interferência da dor, incapacidade da dor e prevalência da síndrome das pernas inquietas em comparação com os controles. Além disso, os pacientes com DP e com sintomas para ansiedade e depressão apresentaram significativamente maior gravidade da dor, interferência da dor e incapacidade de dor, mas não prevalência de SPI, em comparação com apenas pacientes com DP, ansiedade com DP e depressão com DP.
Rana et al., 2016[2]	Observacional caso-controle	40 pessoas com DP (20 solteiros e 20 casados) 40 controles saudáveis (20 solteiros e 20 casados)	Depressão Interferência da dor	HADS BPI	Quando comparado aos grupos controle, o grupo DP (solteiro) apresentou a maior prevalência de depressão, seguido pelo grupo DP (casados), enquanto o grupo controle (solteiro) apresentou prevalência maior do que o grupo controle (casados). Um efeito principal foi encontrado na gravidade da depressão, mas não foram observadas diferenças significativas entre os grupos de DP. Por fim, os pacientes com DP (solteiros) tiveram escores de interfe-

					rência de dor significativamente maiores do que os pacientes com DP (casados).
Rana et al., 2016[3]	Observacional caso-controle	74 pessoas com DP 74 controles saudáveis	Ansiedade Depressão Gravidade e frequência da dor Prevalência da Síndrome das Pernas Inquietas Qualidade do sono	HADS BPI Critérios diagnósticos da SPI. PSQI	Pacientes com DP com dor apresentaram gravidade de ansiedade significativamente maior e pior qualidade do sono do que pacientes com DP sem dor. Comparados aos controles com dor, os pacientes com DP com dor apresentaram mais ansiedade, depressão e piora da qualidade do sono. Pacientes com DP com dor eram mais propensos a relatar dor acatísica, tensional e aguda em comparação com controles com dor, mas essas três características da dor não se correlacionaram entre si. Não houve diferenças na depressão, ansiedade ou sono entre pacientes com DP com acatisia, tensão e dor aguda e aqueles sem.
Rodríguez-Violante et al., 2016	Observacional transversal	341 pessoas com DP	Classificação da DP Dor † SNMs	UPDRS KPPS NMSS	No total, 314 pacientes foram incluídos. No geral, 88,6% da amostra relatou pelo menos 1 tipo de dor. A pontuação padrão média do KPPS foi de 18,8 (DP 19,5). Os fatores associados a maiores pontuações no KPSS foram sexo feminino, tratamento com levodopa, presença de humor deprimido, desgaste e discinesia. Os participantes que apresentavam os

					subtipos motores de instabilidade postural e dificuldade de marcha apresentaram pontuações mais altas no KPPS em comparação com aqueles que apresentavam outros subtipos. A análise de regressão multivariada mostrou que apenas sexo, subtipo motor, humor deprimido e os escores do domínio sono/fadiga da NMSQ alcançaram significância estatística como determinantes.
Buhmann et al., 2017	Observacional transversal	178 pessoas com DP	Ansiedade e depressão Dor (presença, intensidade, duração, localização) Função cognitiva Gravidade da DP Qualidade de vida	HADS Questionário alemão de dor UPDPQ *Paindetect* MMSE Hoehn-Yahr PDQ-39	No geral, a prevalência de dor foi alta (95,4%); 91,1% sofriam de dor crônica, mas em apenas 22,3% deles foi diagnosticado distúrbio de dor. A dor prejudicou a vida cotidiana de forma moderada a muito grave em 48,4% dos pacientes e foi o sintoma mais angustiante em 10,2% de todos os pacientes. A dor localizou-se principalmente nas costas (71,4%) ou articulações (52,4%), ocorreu frequentemente como crises de dor (79%), mas apareceu com caráter neuropático em apenas 15,3% dos pacientes. A maioria dos pacientes (74,2%) recebeu algum tipo de tratamento para a dor, principalmente por ortopedistas (62,0%) ou clínicos gerais (50,0%). Fisioterapia (61,3%), analgésicos (54,4%) ou massagem (35,5%)

					foram as medidas terapêuticas mais frequentes. A terapia de reabilitação (96,3%) e a fisioterapia (89,5%) foram classificadas como mais eficazes, mas com efeitos muito temporários. 53,3% dos pacientes atribuíram a DP como a principal causa de sua dor, mas apenas 33,6% encontraram alívio com drogas antiparkinsonianas. Altos níveis de dor foram associados a maiores escores de depressão e ansiedade e menor qualidade de vida.
Choi et al., 2017[1]	Observacional transversal	161 pessoas com DP	Depressão Estadiamento de DP Função cognitiva Qualidade de vida Sintomas da DP Tipo e intensidade de dor	BDI Hoehn-Yahr K-MMSE K-PDQ-39 UPDRS BPI EVA	Cento e vinte (74,5%) pacientes com DP apresentavam dor crônica. A dor musculoesquelética foi o tipo mais prevalente, seguida da dor radicular/ neuropática, distônica e central. Pacientes com DP com dor, independentemente do subtipo de dor, tiveram pior pontuação no PDQ-39 do que aqueles sem dor. A análise de regressão multivariada após o ajuste para fatores relacionados à doença e características motoras mostrou que a idade de início da DP mais jovem e os altos escores do UBDRS, BDI e EVA foram preditores significativos do PDQ-39 ruim pontuação. A dor, juntamente com a depressão, as atividades de vida diária deficientes e a idade mais jovem de

					início dos sintomas da DP estão associadas a uma qualidade de vida ruim. Todos os subtipos de dor afetam a QV dos pacientes com DP.
Choi et al, 2017[2]	Observacional transversal*	162 pessoas com DP	Depressão DMO Dor Estadiamento da DP Níveis séricos de Cálcio e vit. D SMs	BDI DEXA BPI EVA Autorrelato Hoehn-Yahr Coleta sanguínea UPDRS	Dos 162 pacientes com DP, 120 apresentavam dor crônica, enquanto 42 não relataram dor. O tipo de dor mais prevalente foi musculoesquelético, seguido de radicular/neuropática, distonica e central. Pacientes com DP com dor musculoesquelética apresentaram menor DMO do que pacientes com DP sem dor. A análise de regressão multivariada mostrou que a baixa DMO da coluna lombar, quadril e colo do fêmur estava relacionada à idade avançada, sexo feminino, baixo MBI e presença de dor musculoesquelética
Defazio et al., 2017	Observacional transversal multicêntrico	321 pessoas com DP	Complicações motoras e condições médicas (diabetes mellitus, osteoporose, doença reumática, doença articular degenerativa, artrite e hérnia de disco) que predispõem à dor Dor	Exame clínico e laboratoriais	Na época do estudo, 180 pacientes com DP (56%) relataram dor crônica que, na maioria dos casos, foi descrita como dor muscular ou artrálgica. A dor precedeu o início dos sinais motores em 36/180 pacientes. No modelo de efeito principal, os fatores independentemente associados à dor foram sexo feminino, condições médicas que predispõem à dor, estadiamento Hoehn-Yahr, complicações motoras e NMS pertencentes à sono/fadiga e humor/cognição.

			Gravidade da DP SNMs	Autorrelato Hoehn-Yahr NMSS	A maioria das variáveis explicativas na análise multivariável foi distribuída de forma semelhante em pacientes nos quais a dor pode estar relacionada à DP ou a outra causa que não a DP.
Lien et al., 2017	Observacional coorte retrospectivo	490 pessoas com DP 1960 controles saudáveis	Local da dor Mecanismo da dor Associação com outras doenças	Dados do Banco de Dados de Pesquisa de Seguro Saúde Nacional (NHIRD) de Taiwan	Um total de 490 pacientes com 50 anos ou mais com DP recém-diagnosticada foram identificados durante um período de 2000 a 2005. Entre eles, 199 desenvolveram MSP após DP. O grupo controle foi composto por 1.960 participantes sem DP durante o período do estudo selecionados aleatoriamente por casos de DP correspondentes de acordo com a data de incidência de DP, idade e sexo. Os grupos de estudo foram então acompanhados até o final de 2007. A dor musculoesquelética foi o desfecho. As taxas de incidência de MSP foram maiores no grupo DP do que no grupo controle. A DP foi associada a um risco significativamente elevado de MSP em todas as estratificações de sexo e idade, com a maior taxa de risco observada para pacientes do sexo masculino de meia-idade com DP, seguidos por pacientes do sexo masculino mais velhos com DP.

Ozturk et al., 2017	Observacional transversal	113 pessoas com DP	Ansiedade e depressão Dor† Estágio da DP Fadiga Gravidade clínica/ tratamento da doença Qualidade de vida	DSM-IV EVA Hoehn-Yahr Escala de Severidade de Fadiga UPDRS SF-36	Setenta e três pacientes (64,6%) sofriam de dor crônica. Destes, 12 (16,4%) apresentavam dor prévia no momento do diagnóstico da DP. As fontes de dor experimentadas pelos pacientes foram 89,0% musculoesqueléticas, 31,5% neuropáticas radiculares/periféricas, 15,1% distônicas e 4,1% parkinsonianas centrais, respectivamente. Vinte e seis pacientes (35,6%) apresentaram diferentes tipos de dor simultaneamente. O tipo de dor com maior gravidade foi a dor parkinsoniana central. Os preditores independentes de dor crônica incluíram sexo feminino, UPDRS parte II (atividades da vida diária), subescore de rigidez da UPDRS parte III (sintomas motores) e depressão. Quando comparados com indivíduos sem dor crônica, os escores SF-36 foram menores em pacientes com dor crônica. Além disso, foi demonstrado que o fator mais significativo no SF-36 foi a dor crônica.
Rana et al., 2017	Observacional caso-controle	120 pessoas com DP 120 controles saudáveis	Depressão Intensidade de dor Interferência da dor; Incapacidade da dor	HADS BPI PDI	O estudo encontrou uma correlação direta estatisticamente significativa entre o BPI, PDI e PD. Uma correlação direta significativa também foi encontrada para depressão e dor na DP.

Adewusi et al., 2018	Observacional caso-controle	51 pessoas com DP 51 controles saudáveis	Dor† Dor neuropática periférica Qualidade de vida	KPPS MNSI SF-36	Cinquenta e um pacientes e 51 controles pareados por idade e sexo foram recrutados. A prevalência de dor global foi semelhante nos dois grupos. No entanto, pacientes com DPI apresentaram pontuações mais altas no KPPS em relação à flutuação, noturna e orofacial domínios em relação aos controles. Pacientes com DPI apresentaram mais PNP em comparação com controles saudáveis. Após o ajuste para idade, sexo, duração da doença e pontuação geral do KPSS, o PNP correlacionou-se negativamente com a pontuação de funcionamento físico, pontuação de limitações do papel emocional e pontuação de percepção geral de saúde domínios do SF-36.
Fu et al., 2018	Observacional transversal*	144 pessoas com DP	Depressão Diário do sono Distúrbios do sono Dor† Função cognitiva Qualidade de vida Qualidade do sono SMs	HDRS *Epworth Sleepiness Scale* Polissonografia EVA Relato de localização Relato de uso de terapia farmacológica MMSE PDQ-39 PSQI	A dor foi relatada por 75 pacientes (52,1%), com 49 (65,3%) relatando dor de gravidade pelo menos moderada. Os pacientes com DP com dor eram mais velhos e tinham maior duração da doença, sintomas de DP mais graves, avaliados pelo estágio de Hoehn-Yahr e pela UPDRS, e dose diária equivalente de L-dopa mais alta em comparação com pacientes com DP sem dor. Pacientes com DP com dor também apresentaram redução

			SNMs	UPDRS NMSS	significativa da eficiência do sono, aumento do estágio 1 de movimento ocular não rápido e diminuição do sono de movimento rápido dos olhos. A análise de regressão logística binária revelou que piores atividades da vida diária, humor deprimido, maior porcentagem de sono N1 e menor eficiência do sono foram preditores independentes de dor em pacientes com DP.
Galazky et al., 2018	Observacional caso-controle*	97 pessoas com DP 97 pacientes neurológicos sem o diagnóstico de DP e outras doenças neuromusculares	Intensidade de dor Irradiação da dor Instabilidade vertebral	Questionário estruturado Raio-X	A lombalgia ocorreu significativamente mais frequente na DP (87,6%) em comparação aos controles (62,6%) com maior duração e maior intensidade da dor. A intensidade da dor e os escores de incapacidade foram associados a maiores estágios de DP e maiores escores motores. Pacientes com o subtipo de DP hipocinética experimentaram maior intensidade de dor. A radiografia da coluna lombar revelou artrose lombar em 79,6%, escoliose em 38,8% e espondilolistese em 24,1% dos pacientes com DP com lombalgia. A lateralização da escoliose e os sintomas da DP foram significativamente correlacionados. Apenas uma pequena parcela de pacientes com DP com lom-

					balgia recebeu tratamento ortopédico especializado.
Ozturk & Kocer 2018	Observacional transversal*	168 pessoas com DP 179 controles saudáveis	Ansiedade e depressão Atividade física Fadiga Gravidade da doença Intensidade de dor SMs	HADS Auto-relato de +3x de 60 min/semana Escala de fadiga severa Hohen-Yahr EVA UPDRS	A frequência de dor lombar crônica em pacientes com doença de Parkinson e controles foi de 48,2% e 26,7%, respectivamente. Os fatores de risco preditivos de dor lombar crônica na doença de Parkinson foram fatores gerais, incluindo idade e HADS – subescore de depressão e DP – fatores relacionados, incluindo rigidez e pontuação dos itens de postura.
Rana et al., 2018[1]	Observacional caso-controle	100 pessoas com DP 100 controles saudáveis	Ansiedade Depressão Intensidade de dor Interferência da dor Qualidade do sono Prevalência da Síndrome das Pernas Inquietas	HADS BPI PSQI Critérios de diagnóstico de SPI.	Pacientes com DP com má qualidade do sono apresentaram maior gravidade da dor e interferência da dor do que controles e pacientes com DP com qualidade de sono boa ou limítrofe. Pacientes com DP com má qualidade do sono também apresentaram maior frequência e gravidade para depressão e ansiedade. No entanto, os pacientes com início da DP do lado direito não foram significativamente correlaciona-dos com depressão, ansiedade ou dor.
Rana et al., 2018[2]	Observacional caso-controle	96 pessoas com DP 96 controles saudáveis	Depressão Intensidade de dor Interferência da dor	HADS-D BPI	Foi determinado que os pacientes com DP apresentaram escores de gravidade da dor significativamente mais altos em comparação aos controles. Os pacientes com DP com sintomas depressivos apresentaram escores de intensidade da

					dor e interferência da dor significativamente maiores do que os controles sem sintomas depressivos. Os pacientes com DP relataram maiores pontuações na interferência global da dor do BPI e todos os componentes da subescala de interferência da dor.
Rana et al., 2018[3]	Observacional caso-controle	34 pessoas com com DP 34 pessoas com DP+OA 34 pessoas com OA 34 controles	Ansiedade Depressão Intensidade de dor Interferência da dor	HADS BPI	Pacientes com DP+OA e DP pioraram a gravidade da depressão e eram mais propensos a relatar ansiedade e depressão do que pacientes com OA. Os pacientes com DP+OA eram mais propensos a queixar-se de dor parestésica e acastísica, mas menos propensos a queixar-se de dor em comparação com pacientes com DP e pacientes com OA. Os pacientes DP+OA eram mais propensos a ter maior intensidade de dor e eram mais propensos a relatar dor irradiada e aguda do que os pacientes com início da DP do lado direito. Os pacientes com DP+OA também foram mais propensos a relatar maior caso de depressão do que os pacientes com início da DP do lado direito.
Scalzo et al., 2018	Observacional transversal	45 pessoas com DP	Cognição Depressão Distúrbios do sono Dor†	MMSE BDI PDSS Questionário de McGill EVN	Participaram do estudo 45 pacientes, sendo que 19 (42,2%) apresentavam queixa de dor e, em sua maioria, após o diagnóstico de DP (74%). Não houve diferença entre os grupos com dor e

			Estágio da DP Fadiga SMs	Hoehn-Yahr PFS-16 UPDRS	sem dor para os parâmetros clínicos avaliados, com exceção da fadiga que foi mais prevalente e mais grave nos pacientes com dor.
Silva et al., 2018	Observacional transversal	77 pessoas com DP	Apertamento/rangido diurno Dor † Mordida desconfortável/não habitual Rigidez matinal Zumbido Estalido Gravidade da DP	Autorrelato Critério de Diagnóstico de Pesquisa para Distúrbios Temporomandibulares Hoehn-Yahr	Foram avaliadas 139 pessoas com doença de Parkinson. Dessas, 77 encontraram-se dentro dos critérios de elegibilidade, sendo que 70% da amostra era do sexo masculino, com média de idade de 62±9 anos, tempo de diagnóstico da doença de Parkinson de 6±4 anos e com 71% da amostra no estágio moderado. Não foram encontradas associações significativas entre a idade, sexo, tempo e estágio da doença com a disfunção temporomandibular. Das variáveis analisadas, os resultados significativos mostraram que a presença de dor representa uma maior chance de desenvolver a disfunção temporomandibular, a crepitação reflete uma precisão moderada na classificação do transtorno da articulação temporomandibular e o estalido aumenta a probabilidade de ter a disfunção temporomandibular.
Silverdale et al., 2018	Observacional transversal multicêntrico	1957 pessoas com DP	Ansiedade e depressão Características e intensidade da dor	Escala de Ansiedade e Depressão de Leeds SFMPQ EVA	85% dos participantes relataram dor (42% com dor moderada a intensa). A dor influenciou a qualidade de vida mais do que os sintomas motores em

				KPPS	um modelo de regressão múltipla. Os fatores que predizem a gravidade geral da dor incluíram sintomas afetivos, sintomas autonômicos, complicações motoras, sexo feminino e idade mais jovem, mas não comprometimento motor ou duração da doença. Houve correlação insignificante entre a gravidade do comprometimento motor e a gravidade da dor musculoesque-lética ou distônica, bem como entre a gravidade dos problemas motores do período *Off* e a gravidade da dor do período *Off* ou dor distônica do período *Off*. Características de sensibilização central, incluindo alodinia e sensação de dor alterada foram comuns nesta população. O uso de medicamentos direcionados à dor central foi muito baixo.
			Dor neuropática	LANSS	
			Função cognitiva	MoCA	
			Qualidade de vida	EQ-5D	
			Sintomas autonômicos	Escala para Resultado na DP – Sintomas Autonômicos	
				UPDRS	
			SMs e SNMs		
Suzuki et al., 2018	Observacional caso-controle multicentrico	436 pessoas com DP 401 controles saudáveis	Distúrbios do sono	PDSS-2	Os pacientes com DP tiveram prevalências de enxaqueca ao longo da vida e 1 ano menores do que os controles. No entanto, a prevalência de cefaleia ao longo da vida e 1 ano não diferiu entre pacientes com DP e controles. Após o ajuste para sexo, momento da avaliação das alterações da cefaleia e período de recuperação, os pacientes com DP com cefaleias ou
				ESS	
				Questionário de Triagem do Transtorno do Comportamento do Sono	
				PSQI	
			Enxaqueca	Questionário semi-estruturado	
				Hoehn-Yahr	

			Gravidade da doença Hábitos, educação, estado de sono e dores de cabeça Intensidade de dor SMs Transtornos mentais	Questionário estruturado EVA UPDRS Mini Entrevista Neuropsiquiátrica Internacional semiestruturada	enxaquecas exibiram uma redução pronunciada na intensidade, frequência e gravidade geral de suas cefaleias e enxaquecas após o início da DP em comparação com controles com cefaleias ou enxaquecas. Pacientes com DP com enxaqueca exibiram uma taxa mais alta de depressão e maiores pontuações do PSQI do que aqueles sem dores de cabeça.
Zella et al., 2018	Observacional transversal*	2814 pessoas com DP	Características da dor	Questionário estruturado	O estudo incluiu 1.204 pacientes do sexo feminino e 1.610 do sexo masculino. A dor espinal-paravertebral emergiu como a forma dominante de dor. Uma correlação significativa foi demonstrada ainda entre gênero e localização da dor, intensidade da dor e dor como comprometimento da qualidade de vida. Os anti-inflamatórios não esteroides foram os analgésicos mais utilizados pelos pacientes. Além dos analgésicos não opioides, não foi demonstrada correlação significativa entre os tratamentos da dor e o sexo.
Alwardat et al., 2019[1]	Observacional transversal	48 pessoas com DP	Dor† Estadiamento da DP Função cognitiva Função específica das costas	BPI UPDRS MMSE ODI	Os grupos PS e C&A apresentaram significativamente pior incapacidade ODI e dor BPI, e maior estágio LEDD e Hoehn-Yahr em comparação com os grupos DP. No entanto, não foram encontradas diferenças na duração da

			Gravidade da DP	Hoehn-Yahr	DP e UPDRS nos mesmos grupos. Além disso, não foram observadas diferenças entre os grupos PS e C&A nas escalas mencionadas.
Alwardat et al., 2019[2]	Observacional transversal	45 pessoas com DP	Dor† Dor no pescoço Estadiamento da DP Função cognitiva Gravidade da DP	BPI Neck Disability Index UPDRS MMSE Hoehn-Yahr	O grupo DP comparado com os grupos PS e C&A apresentou diferenças no estadiamento NDI, BPI-MAS, BPI-PI, LEDD e Hoehn-Yahr, mas não foram encontradas diferenças na duração do DP, UPDRS-II e III nos mesmos grupos. Além disso, não foram observadas diferenças entre os grupos PS e C&A nas escalas mencionadas.
De Mattos et al., 2019	Observacional transversal	54 pessoas com DP	Dor † Marcha Equilíbrio SMs	KPPS BPI Dynamic Gait Index *Mini-BESTest* UPDRS	Trinta e oito participantes (70,3%) relataram dor leve a moderada. Uma correlação positiva foi encontrada entre a pontuação total do KPPS e o desempenho em atividades gerais do UPDRS II; foi encontrada uma correlação negativa entre a intensidade da dor do BPI e a função motora do UPDRS III; e uma correlação negativa foi encontrada entre a intensidade da dor do BPI e o subescore de bradicinesia da UPDRS III. Não houve correlação entre dor e desempenho da marcha ou equilíbrio. A dor musculoesquelética foi o tipo predominante (em 81,5% dos indivíduos), seguido de dor noturna (52,6%) e dor relacionada à

					flutuação (47,3%). As áreas mais dolorosas foram membros inferiores (33,0%) e ombros/região cervical (31,0%). Vinte e um dos 38 participantes (55,3%) relataram interferência da dor em sua capacidade de trabalho e marcha e atividades gerais.
Hirsi et al., 2019	Observacional transversal	103 pessoas com DP	Depressão Dor†	*Patient Health Questionairre-9* KPPS	Foram estudados 103 pacientes com DP. Destes, 87 (84%) apresentaram sintomas de dor. Apenas 16 (18,4%) receberam medicações para dor, porém ninguém foi encaminhado para fisioterapia.
Joseph et al., 2019	Observacional transversal	100 pessoas com DP 47 controles saudáveis	Depressão Dor Equilíbrio Função cognitiva Gravidade da doença Qualidade de vida SMs	*Geriatric Depression Scale 20* Domínio dor do SF-36 *Mini-BESTest* MMSE Hoehn-Yahr PDQ-39 UPDRS	A gravidade da dor foi significativamente maior em pessoas com doença de Parkinson do que controles saudáveis. Entre as pessoas com doença de Parkinson, o modelo preditor multivariado, explicando 34% da variação nos escores de gravidade da dor, identificou três fatores associados independentemente. Pior desempenho de equilíbrio, menor duração da doença e pior qualidade de vida relacionada à saúde foram independentemente associados à gravidade da dor. A gravidade da dor é maior naqueles que vivem com DP do que nos controles, e a gravidade parece estar associada às características da doença e à saúde geral.

Martinez-Martin et al., 2019	Observacional transversal multicêntrico	300 pessoas com DP	Ansiedade e depressão Distúrbios do sono Dor† Gravidade da doença Qualidade de vida SMs SNMs	HADS PDSS-2 EVA KPPS KPPQ Hoehn-Yahr Índice de Impressão Clínica de Gravidade para PD EQ-5D-3L PDQ-8 *Scales for Outcomes in Parkinson's Disease-Motor* NMSS	De acordo com o PDSS-2, 99,3% da amostra sofria de pelo menos um problema de sono. Aqueles que relataram experimentar qualquer modalidade de dor sofreram significativamente mais de distúrbios do sono do que aqueles que não. O PDSS-2 apresentou correlações moderadas a altas com o KPPS, KPPQ e EVA. Quando os itens 10 a 12 do PDSS-2 (relacionados à dor) foram excluídos, os valores de correlação diminuíram, enquanto esses itens mostraram correlações moderadas a altas com KPPS, KPPQ e EVA. Entre as variáveis analisadas, modelos de regressão linear múltipla sugeriram que KPPS e KPPQ foram os preditores mais relevantes de distúrbios do sono (de acordo com o PDSS-2), embora após a exclusão dos itens de dor do PDSS-2, a depressão foi o preditor relevante. Depressão e ansiedade foram os preditores mais relevantes na análise envolvendo a EVA-Dor. A análise de regressão, considerando apenas os domínios do KPPS, mostrou que as dores noturnas e musculoesqueléticas foram os melhores preditores de distúrbio geral do sono noturno.

Rana et al., 2019	Observacional caso-controle*	88 pessoas com DP 88 controles saudáveis	Depressão Distúrbios do sono Dor†	HADS PSQI BPI PDI	DP-indianos não diferiram de DP-caucasianos em ansiedade ou depressão. No entanto, os DP-caucasianos eram mais propensos a relatar dor dolorosa em 80 vezes e dor incômoda em 108 vezes em comparação com os DP-indianos. Os DP-indianos eram 82% menos propensos a ter dor interferindo nas atividades sociais e 90% menos propensos a ter dor interferindo nas relações com os outros em comparação com os DP-caucasianos.
Vila-Chã et al., 2019[1]	Observacional transversal	229 pessoas com DP	Ansiedade e depressão Distúrbios do sono Dor Gravidade da DP SMs	HADS PDSS-2 Questionário Hoehn-Yarh UPDRS	Setenta e cinco (33%) pacientes apresentaram distúrbios do sono clinicamente relevantes (PDSS-2≥18) e 162 pacientes (71%) relataram dor. Daqueles com dor, 38 (24%) tinham dor parkinsoniana central. Pacientes com DP com distúrbios do sono apresentaram mais dor e sintomas motores mais graves, menor independência funcional, mais sintomas de ansiedade e depressão e pior qualidade de vida. Entre os pacientes com dor, a dor parkinsoniana central foi o subtipo de dor com maior chance de distúrbios do sono, mesmo levando em consideração sintomas motores (Hoehn-Yarh *off*), flutuações motoras, intensidade da

					dor (BPI) e sintomas de ansiedade e depressão (HADS).
Vila-Chã et al., 2019[2]	Observacional transversal	292 pessoas com DP	Ansiedade e depressão Dor† Estado *On* e *Off* Freezing de marcha Gravidade da DP Síndrome de desregulação dopaminérgica SMs	HADS BPI PDI Questionário estruturado Escala de Independência de Schwab e Inglaterra FOG-Q Hoehn-Yahr Questionário de Transtornos Impulsivos Compulsivos em DP de corrente curta UPDRS	Duzentos e doze pacientes (73%) relataram dor, que foi classificada como: musculoesquelética (63%), relacionada à distonia (27%), parkinsoniana central (22%) e/ou radicular ou neuropática (9%). Os pacientes com dor apresentaram mais comorbidades e sintomas motores mais graves. Os pacientes com dor parkinsoniana central eram significativamente mais jovens, tinham início mais precoce da doença, menos comorbidades, maior gravidade dos sintomas motores não-axiais, mais incapacidade relacionada à dor e mais alívio da dor com medicação antiparkinsoniana do que pacientes com dor parkinsoniana não central.
Cruz-Almeida et al., 2020	Observacional transversal*	113 pessoas com DP 60 controles	Comorbidade da DP Depressão Fenótipos cognitivos	Escala de comorbidade Charlson Escala de Depressão Geriátrica Funções executivas e medidas de memória episódica WAIS-III Sequência de Números de Letras e Testes de Símbolos de Dígitos	Os participantes com DP com baixa função executiva relataram interferência da dor significativamente maior, apesar de relatarem níveis de gravidade da dor semelhantes em comparação com outros fenótipos. Essas diferenças permaneceram estatisticamente significativas, mesmo após contabilizar fatores de confusão importantes, como ansiedade e depressão.

				Teste de Cor-Palavra de Stroop Teste de palavra-cor *Trail Making Teste* Parte B Teste de Aprendizagem Verbal Hopkins Medidas de discriminação de reconhecimento e atraso revisados WMS-III Recuperação de atraso de memória lógica	
			Intensidade de dor Interferência da dor SMs	BPI UPDRS	
Faccio et al., 2020	Observacional transversal	81 pessoas com DP	Depressão Dor crônica† DTM Sintomas físicos inespecíficos	Cassificação de dor crônica com base nos Critérios de Diagnóstico de Pesquisa para Distúrbios Temporomandibulares (RDC/DTM)	Um total de 81 idosos atendeu aos critérios de elegibilidade – 67% eram do sexo masculino, 74% eram casados ou tinham companheiro, 43% relataram ganhar de 1 a 2 salários mínimos e 47% estavam no estágio moderado da DP. A DTM foi identificada em 22% da amostra, 12% relatando dor crônica. A análise estatística mostrou associação entre DTM e dor crônica e entre DTM e depressão moderada a grave.
Florin et al., 2020	Observacional transversal*	20 pessoas com DP	Demência	*Mattis Dementia Rating Scale*	A levodopa aumentou a inibição da dor endógena em termos de intensidade da

			Depressão Latência térmica de dor Tolerância à dor térmica Somação temporal SMs	BDI Contato térmico Método de escada modificado com feedback verbal EVA KPPS *PainDETECT* UPDRS	dor percebida e desagrado em comparação com um estado sem medicação. Maior dor clínica foi associada a maiores aumentos na inibição da dor. A levodopa não afetou o limiar de dor ao calor, tolerância ou somação temporal.
Geroin et al., 2020	Observacional transversal	283 pessoas com DP	Dor Grau de flexão de tronco Limitação nas AVDs e SMs	END Goniômetro de parede Medidas baseadas em software (SBM) com o programa freeware Kinovea UPDRS	Foram encontradas associações significativas entre estágio de Hoehn-Yahr modificado, duração da doença, sexo e limitação nas AVDs, comprometimento motor, intensidade da dor nas costas e histórico de quedas. O grau de flexão do tronco foi associado apenas ao comprometimento motor em flexão lateral do tronco. As curvas de características de operação do receptor mostraram que pacientes com flexão lateral do tronco de 10,5º podem apresentar comprometimento motor moderado/grave.
Ghosh et al., 2020	Observacional transversal	167 pessoas com DP	Depressão Dor† Gravidade da DP SMs	BDI BPI KPPS Hoehn-Yahr UPDRS	A prevalência de dor foi de 88,6%, não se correlacionou com idade, gravidade motora (UPDRS parte III) ou duração da doença, enquanto que uma correlação fraca com sexo feminino e estágio Hoehn-Yahr>2,5 foi encontrada. Múlti-

			SNMs, disautonomia e aspectos específicos da qualidade do sono	NMSS	plos SNM correlacionaram-se significativamente com a dor. Especificamente, o distúrbio do sono teve a correlação mais forte com a dor, seguido pela depressão, distúrbios gastrointestinais e cardiovasculares. Análises posteriores mostraram que o sono e os distúrbios cardiovasculares estavam independentemente associados à dor e que esses sintomas se agrupavam em um subconjunto de pacientes com DP. A relação entre dor, sono e disautonomia persistiu independentemente da terapia de reposição de dopamina.
Gonçalves et al., 2020	Observacional transversal	123 pessoas com DP	Dados demográficos Intensidade de dor	Questionário estruturado EVA	Cento e vinte e três pacientes com idade média de 68,1±11,8 anos e duração média da doença de 7,0±4,9 anos responderam o questionário. A dor foi relatada por 102 (82,9%) pacientes: 71 (57,7%) com dor lombar e 31 (25,2%) com dor em outros segmentos corporais. Não houve diferença quanto à idade, escolaridade, tempo de sintomas e de diagnóstico da doença de Parkinson ao comparar os indivíduos com e sem dor, assim como indivíduos com dor em outras regiões e dor lombar. O grupo com dor lombar queixava-se de dor em maior número

					de segmentos corporais além da região lombar, com maior tempo de duração desse sintoma e uso mais frequente de analgésicos. Dentre os indivíduos do grupo com dor lombar, as mulheres apresentavam maior intensidade da dor.
Kobylecki et al., 2020	Observacional transversal*	1909 pessoas com DP	Controle impulsivo da doença Dor neuropática e nociceptiva Intensidade de dor	*Questionnaire for Impulsive-Compulsive Disorders in PD* LANSS EVA KPPS Questionário de McGill	A maioria dos pacientes relatou dor, que foi classificada em 76,6% como nociceptivas, enquanto 8,3% apresentavam dor neuropática. O ICB foi relatado por 25% da população. A dose equivalente de levodopa foi maior nos participantes com qualquer ICB em comparação com aqueles sem. Os participantes com qualquer ICB pontuaram mais alto em todas as escalas de dor e eram mais propensos a ter dor alta e dor neuropática.
Nguy, 2020	Observacional transversal	52 pessoas com DP	Ansiedade e depressão Atividade física Gravidade da DP Intensidade de dor Interferência da dor Qualidade do sono Sensibilização central	HADS Questionário de Exercício Incidental e Planejado UPDRS KPPS BPI PSQI Inventário de Sensibilização Central	Análises de regressão univariada mostraram que o aumento da gravidade da doença, maior duração da doença, maior sensibilização central, aumento da atividade física, sono ruim, ansiedade e depressão foram associados a pior dor em uma ou mais medidas de dor. Os modelos de regressão multivariada foram responsáveis por 56% da variância da KPPS, 25% da gravidade da dor e 36% da interferência da dor. O sono ruim contribuiu inde-

					pendentemente para os piores escores de dor em todos os modelos.
Rocha-Filho & Souza-Lima, 2020	Observacional transversal	46 pessoas com DP	Ansiedade e depressão Dor† Rigidez do pescoço	HADS Questionário estruturado	Cerca de 46 pacientes foram incluídos, 52% eram homens, a média de idade foi de 66 ± 11 anos. Quarenta e três pacientes tiveram dores de cabeça, 12 (26%), enxaquecas, 31 (67%) tiveram dores de cabeça do tipo tensional. Não encontramos associação entre a frequência de cefaleia ou intensidade e os diferentes estágios da DP. Não houve correlação entre a pontuação UPDRS e a intensidade ou frequência de dores de cabeça. Não foi encontrada associação entre o grau de rigidez de nuca e a frequência de cefaleia ou intensidade. Doze pacientes disseram que suas dores de cabeça começaram após o diagnóstico de DP. Não houve diferença quanto à frequência e características das cefaleias e caracte-resticas da DP entre esses pacientes e os demais pacientes com cefaleias prévias.
Silveira Barezania et al., 2020	Observacional transversal	115 pessoas com DP	Capacidade de contrair o transverso abdominal Características epidemiológicas Função cognitiva	Teste prono com o esfigmomanômetro Questionário epidemiológico MMSE	Cento e quinze pacientes responderam ao questionário e 95 (82,6%) relataram sintomas dolorosos. Destes, 67 (58,3%) apresentavam lombalgia crônica e aproximadamente 40% dos pacientes relataram seu início antes do diagnós-tico de DP. Escores mais altos de

			Incapacidade relacionada à lombalgia na DP Depressão Gravidade da DP Medidas quantitativas da lombalgia clínica Qualidade de vida SMs	Questionário de Incapacidade de Roland Morris BDI Hoehn-Yahr Questionário de McGill PDQ-39 UPDRS	intensidade de dor, sintomas depressivos e UPDRS II e III, estágios mais avançados da DP e ausência de contração do TrA determinaram a limitação funcional induzida pela lombalgia. No entanto, a intensidade da dor (McGill), a gravidade dos sintomas da DP (UPDRS III) e a ausência de contração do TrA foram identificados como fatores preditivos de limitação funcional e explicaram 66,1% da variância do RMDQ. Intensidade da dor e a incapacidade relacionada à lombalgia causou impacto negativo na qualidade de vida.
Sung et al., 2020	Observacional transversal	25 pessoas com DP	Afeto Depressão Desenvolvimento de medicamentos flutuações induzidas e discinesia Gravidade da DP Limiar de dor à pressão Intensidade de dor Classificações da dor	PANAS Escala Geriátrica de Depressão WOQ-9 MAIMS UPDRS LDP END RM functional	Os participantes da DP discinética experimentaram aumento da sensibilidade à dor à pressão. Isso foi associado ao aumento da dor induzida por pressão, atividade BOLD inócua em áreas associadas à codificação da intensidade da dor, orientação espacial da dor, mediação descendente da dor, integração sensório-motora e controle motor. A levodopa reduziu as classificações de dor por pressão e melhorou o afeto negativo, embora não tenha afetado a atividade BOLD de maneira diferente entre os grupos.

			Nível de oxigênio dependente no sangue regional Presença de dor clínica† Qualidade de vida	Pressão fásica SFMPQ PDQ-39 PDY-26	
Walmsley et al., 2020	Observacional transversal	120 pessoas com DP 76 fisioterapeutas	Dados demográficos História da DP Distúrbios e dores no ombro Conhecimento dos fisioterapeutas sobre o manejo dos distúrbios e dores no ombro de pessoas com DP	Questionário estruturado	Uma pesquisa postal foi enviada a 189 pacientes com DP e uma pesquisa online foi enviada por e-mail a 336 fisioterapeutas. Uma taxa de resposta de 63% foi obtida para pacientes com DP e 23% para fisioterapeutas. Dos pacientes com DP, 13% relataram início de dor e/ou rigidez no ombro dentro de 5 anos antes do diagnóstico, sem história pregressa de problemas no ombro. Desses pacientes, 8% relataram especificamente sintomas no ombro como manifestação inicial da doença. No entanto, 74% dos fisioterapeutas pesquisados desconheciam o potencial de apresentação precoce desse sintoma.
Yilmaz et al., 2020	Observacional transversal*	110 pessoas com DP	Freezing de marcha Gravidade da doença Intensidade de dor SMs	FOG-Q Hoehn-Yarh EVA UPDRS	Cinquenta e oito dos pacientes tiveram FOG e 43 sofreram quedas. Entre os pacientes, 42 não apresentavam dor, enquanto 35 apresentavam dor nos membros inferiores. Escores motores UPDRS e FOG mais altos e doença em estágio avançado foram observados em

					um número significativamente maior de pacientes com FOG e quedas. Os escores EVA não foram afetados pela presença de FOG ou quedas. Houve correlação positiva entre a gravidade do FOG e o escore EVA nos pacientes do sexo masculino. Mais pacientes com quedas apresentaram dor nos membros inferiores do que aqueles sem quedas.
Agrawal et al., 2021	Observacional transversal	100 pessoas com DP	Estágio e a gravidade da DP Dor† Qualidade de vida	UPDRS KPPS PDQ-8	A prevalência de diferentes tipos de dor em pacientes com DP foi de 70%, incluindo principalmente musculoes-quelética (53%), relacionada à flutuação (35%) e dor noturna (27%). Indivíduos com dor desenvolveram sintomas de DP em idade mais jovem e tiveram maior duração da doença. Uma correlação positiva foi encontrada entre os escores KPPS e UPDRS partes III e V, enquanto uma correlação negativa foi observada com UPDRS parte VI. A dor em indivíduos com DP teve um impacto significativo na QV.
Kinugawa et al., 2021	Observacional transversal	24 pessoas com DP	Dor † Eletroencefalogra-fia	UPDRS Sistema internacional de colocação de eletrodos 10-20 e uma taxa de amostragem de 200 Hz	Vinte e quatro pacientes com DP esporádica foram avaliados quanto à presença de dor. Análises de tempo-frequência e coerência foram realizadas em seus dados de EEG. A coerência cerebral total e regional foi calculada e comparada entre pacientes com dor

					positiva e dor negativa. Não houve diferença significativa na coerência do cérebro inteiro entre os grupos de dor positiva e dor negativa. No entanto, a coerência temporal-temporal diferiu significativamente entre os dois grupos. Nossos achados indicam que a sincronização aberrante das regiões intertemporais está envolvida na dor relacionada à DP.
Kurihara et al., 2021	Observacional transversal retrospectivo	31 pessoas com DP	Função cognitiva Depressão Desgaste Gravidade da DP Qualidade de vida SMs	MoCA MMSE Escala de autoavaliação de depressão de Zung WOQ-9 Hoehn-Yarh PDQ-8 UPDRS	Neste estudo, 331 pacientes com DP foram classificados em três grupos: grupo sem dor (67,4%), grupo com dor não flutuante (22,1%) e grupo com dor flutuante (10,6%). Avaliamos o histórico dos pacientes e seu impacto na QV de cada grupo. O grupo com dor apresentou maiores níveis de depressão, maior frequência de alucinações visuais e menor QV em comparação com o grupo sem dor. O grupo de dor flutuante teve início mais jovem, estágio Hoehn-Yahr mais alto e maior frequência de desgaste e discinesia do que os outros grupos. Comparamos o índice resumido do PDQ-8 em cada grupo de dor com o grupo sem dor usando análise de variância. Como resultado, o PDQ-8 foi significativa-

					mente maior em ambos os grupos de dor não flutuante e flutuante.
Liguori et al., 2021	Observacional transversal	26 pessoas com DP	Ansiedade Avaliação funcional Bateria neuropsicológica Comprometimento Cognitivo Leve Depressão Dor † Fadiga Funcionamento cognitivo Sonolência diária	Escala de Ansiedade de Parkinson Tesde de caminhada de 10 metros TUG G-walk Teste de realização de teste A Teste de classificação de cartões modificado Teste de evocação em prosa Teste de Aprendizagem Verbal Auditiva de Rey Cópia de desenhos Teste de Julgamento de Orientação de Linha Nível II da Força-Tarefa da Sociedade de Distúrbios do Movimento BDI KPPS Escala de gravidade da fadiga de Parkinson MoCA ESS	A fadiga teve uma correlação negativa moderada com a cadência do passo e uma correlação positiva moderada a forte com a duração da marcha, TUG e TUG *Dual Task*. A dor apresentou correlação positiva moderada com a duração da marcha. Doze pacientes apresentaram comprometimento cognitivo leve e relataram escores significativamente piores na duração da marcha, dor e fadiga. De acordo com os escores z cognitivos, o grupo com comprometimento cognitivo leve apresentou correlação negativa moderada entre habilidades visuoespaciais e fadiga.

			SMs	UPDRS	
Lopes et al., 2021	Observacional caso-controle	34 pessoas com DP	Gravidade da DP Intensidade de dor	Hoehn-Yahr END	A intensidade média da dor entre aqueles em uso de medicação (2,17±0,39) foi significativamente menor do que no grupo de abstinência (4,2±0,59) o que correspondeu ao aumento do escore total do estadiamento funcional de 93 a 111, respectivamente.
Naisby et al., 2021	Observacional transversal*	154 pessoas com DP 99 controles	Depressão Dor† Função cognitiva Gravidade da DP SMs	Escala de Depressão Geriátrica NMSQ Domínio dor do PDQ-39 MMSE MoCA Hoehn-Yahr UPDRS	A dor inexplicável foi comum no grupo DP e ocorreu com mais frequência do que nos controles pareados por idade. 'Sofrimentos e dores' ocorreram com mais frequência do que 'cãibras e espasmos musculares' em cada ponto de tempo, exceto 54 meses.
O'Neill et al., 2021	Observacional transversal	1916 pessoas com DP	Depressão Dor† SMs	Escala de Ansiedade e Depressão de Leeds KPPS EVA Questionário de McGill LANSS UPDRS	Um total de 139 (7,3%) pacientes relatou a presença de alguma forma de dor orofacial. A síndrome da ardência bucal foi relatada em 32 (1,7%), enquanto a mastigação foi encontrada em 38 (2,0%) e a mastigação em 78 (4,0%). A dor orofacial foi significativamente mais comum no sexo feminino (10,4%) do que no sexo masculino (5,9%). A análise de regressão logística múltipla mostrou associação significativa entre dor

					orofacial e intensidade da dor, dor neuropática e disfunção motora oral e não motora.
Paul et al., 2021	Observacional transversal	127 pessoas com DP	Diagnóstico de Síndrome das Pernas Inquietas Dor † Interferência de dor Percepção da dor	Critérios de diagnóstico de Síndrome das Pernas Inquietas Entrevista semiestruturada BPI	Os resultados demonstraram que o paciente com doença de Parkinson que relatou dor obteve 23 pontos a mais de prevalência da SPI e 8,5 contagens a mais para a gravidade da SPI em comparação com o grupo de pacientes com DP que negaram dor.
Prell et al., 2021	Observacional transversal*	52 pessoas com DP	Classificação da dor Depressão Enfrentamento da dor Função cognitiva Qualidade de vida Sintomas	Domínio dor do SF-36 BDI *Coping Strategy Questionnaire* SF-36 MoCA Hoehn-Yahr NMSQ UPDRS	A maioria dos pacientes lida com a dor por meio de estratégias cognitivas ativas (auto-afirmações de enfrenta-mento) e comportamentais ativas (aumentando os comportamentos de dor e aumentando o nível de atividade). O enfrentamento ativo foi associado com menor índice de dor. Em relação aos domínios da QV, o coping ativo foi associado a melhor funcionamento físico e melhor energia, enquanto o coping passivo foi associado a pior bem-estar emocional. No entanto, conforme demonstrado pela MANOVA, o impacto dos fatores de enfrentamento (ativo e passivo) nos domínios SF-36 foi insignificante após correção para idade, função motora e depressão

Vila-Chã et al., 2021	Observacional transversal	260 pessoas com DP	Classificação da dor Distúrbios de controle de impulsos, outros comportamentos compulsivos e uso compulsivo de medicação Sintomas	Classificação de Ford Questionário para Distúrbios de Controle de Impulsos na Forma Curta da Doença de Parkinson UPDRS	Cento e oitenta e oito pacientes (68%) relataram dor; e em 41 (22%) deles, a dor foi classificada como dor parkinsoniana central. Pacientes com DP com dor parkinsoniana central tiveram melhor desempenho cognitivo nas subescalas de Iniciação/Persevera-ção e Conceituação do Questionário para Distúrbios de Controle de Impulsos na Forma Curta da Doença de Parkinson, mas relataram mais outros comportamentos compulsivos e tinham mais hábitos de fumar atuais do que aqueles sem dor ou com não dor parkinsoniana central. Apenas os pacientes com dor, independentemente do tipo, apresentavam transtorno de jogo.
Gao et al., 2022	Observacional transversal	88 pessoas com DP	Ansiedade Atividades de vida diária Depressão Dor† Função cognitiva Gravidade da DP Qualidade do sono SMs	HAMA Escala de atividades de vida diária HAMD KPPS EVA MMSE Hoehn-Yahr PSQI UPDRS	A prevalência de distúrbios do sono foi de 76,1% em pacientes com dor relacionada à DP. Entre esses pacientes, o grupo de sono ruim apresentou sintomas motores mais graves, mais sintomas de ansiedade e depressão, menor independência funcional e maior intensidade de dor, como dor musculoesquelética, dor crônica, dor relacionada à flutuação, dor noturna e descoloração/edema/ inchaço. Além disso, os escores do

					PSQI se correlacio-naram positivamente com os escores de todos os 7 domínios do KPPS. O estágio Hoehn-Yahr e o PSQI foram variáveis independentes significativas explicando 50,0% da variância nos escores do KPPS.
Gültekin et al., 2022	Observacional caso-controle restropectivo	55 pessoas com DP 20 controles saudáveis	AVDs Depressão Fadiga Incapacidade da DP Gravidade da DP Estado funcional e incapacidade Intensidade da dor Mobilidade da coluna vertebral	Escala de atividades de vida diária BDI Escala de gravidade fadiga UPDRS Hoehn-Yahr Questionário de deficiência de Roland Morris ODI EVA Teste de Schober modificado-modificado Amplitude de movimento de flexão e extensão lombar	Descobrimos que os valores de MMST e ADM de flexão e extensão foram significativamente diminuídos no gru-po de pacientes em comparação aos controles. Os valores do estágio Hoehn-Yahr, UPDRS, Questionário de deficiência de Roland Morris, ODI e VAS foram maiores e os resultados do MMST foram menores em pacientes com lombalgia do que em pacientes sem lombalgia. Na análise multiva-riada, a presença de lombalgia não se correlacionou com nenhum dos parâmetros, incluindo idade, sexo, duração da doença, sintoma dominante, AVD, depressão e gravidade da fadiga.
Kinugawa et al., 2022	Observacional transversal*	24 pessoas com DP	Função cognitiva Intensidade de dor SMs	MMSE END SFMPQ UPDRS RM	Avaliamos 23 pacientes com DP esporádica com base em ressonância magnética funcional e intensidade da dor usando o SFMPQ revisado. Pacientes com DP apresentaram

					escores de intensidade de dor mais altos no estado "*Off*" do que no estado "*On*". A intensidade da dor no estado "*off*" foi substancialmente correlacionada com a conectividade funcional entre o núcleo accumbens e os córtices motor/sem-sorial primário e o núcleo accumbens contralateral. As mudanças na intensidade da dor do estado "*On*" para o estado "*Off*" exibiram correlações com aquelas entre o núcleo accumbens direito e núcleo accumbens esquerdo e o giro pré-central direito /córtex insular direito do "*Off*" para o estado "*Off*". Núcleo accumbens bilateral aberrante e núcleo accumbens direito– giro pré-central direito/ córtex insular direito conectividade funcional no estado "*Off*" estavam intimamente relaciona-dos aos sintomas de dor desenvolvidos dos estados "*On*" para "*Off*".
Li et al., 2022	Observacional transversal	452 pessoas com DP	Ansiedade Depressão Duração e local da dor Intensidade de dor Qualidade do sono Qualidade de vida	HAMA HAMD Autorrelato Classificação de Ford END PDSS PDQ-39	Duzentos e seis pacientes (45,58%) relataram dor musculoesquelética, geralmente em membros inferiores e dorso. A levodopa resultou em uma redução de 30% nos escores de intensidade da dor em 170 indivíduos. Sexo feminino e doses diárias equivalentes à levodopa foram associa-dos com risco aumentado de dor

					musculoesquelética. A duração da dor, sintomas motores e depressão foram significativamente associados à qualidade de vida.
Samanci et al., 2022	Observacional transversal retrospectivo	86 pessoas com DP	SNMs, data de início, queixas de dor, tipo de dor e local de dor	Autorrelato Classificação de Ford	Oitenta e seis pacientes foram incluídos (42 mulheres, 44 homens). As primeiras queixas foram bradicinesia, tremor, tremor e bradicinesia, dor no ombro, tremor e cãibras dolorosas. Essas queixas começaram há 10,1±5,22 anos e o diagnóstico de DP foi feito em média há 8,56±4,87 anos. Os primeiros departamentos especializados aos quais os pacientes com essas queixas se candidataram foram Neurologia (n=34), Fisioterapia e Reabilitação (n=34), Neurocirurgia (n=10) e Ortopedia (n=8). A primeira admissão em Neurologia foi há 8,7±4,85 anos. As queixas de dor começaram 7,2±6,69 anos antes da primeira internação em 56 pacientes. A dor musculoesquelética foi de 86%, a dor distônica foi de 25%, a dor central e a dor neuropática foram 11% cada no grupo de pacientes que apresentaram dor.
Sung & Kang, 2022	Observacional transversal*	236 pessoas com DP 42 pessoas com atrofia de	Depressão Dor central ou primária Função cognitiva	BDI Definição com base na literatura K-MMSE	Não foi observada diferença na presença de dor, gravidade ou tipo entre os quatro grupos. No entanto, a relação temporal entre dor e sintomas motores

		múltiplos sistemas 31 paralisia supranuclear progressiva 38 parkinso-nismo vascular	Gravidade da DP Gravidade de dor Local da dor Tipo de dor SMs	Hoehn-Yahr EVA Autorrelato Classificação de Ford UPDRS	diferiu. A dor antecedeu os sintomas motores na DP, paralisia supranuclear progressiva e parkinsonismo vascular, mas muitas vezes seguiu os sintomas motores na PSP. A localização da dor no corpo foi diferente entre os quatro grupos de pacientes, e o envolvimento da perna foi mais comum na PSP.

*Tipos de estudo com base na opinião dos autores (EOM e MIOD) devido esta informação estar ausente, ambígua ou incompleta no estudo citado; † Variáveis e instrumentos conforme indicado pelos autores dos estudos incluídos, mas sem correspondência com instrumento padrão ouro reconhecido na literatura.

AVD´s: Atividades de Vida Diária; BDI: Inventário de Depressão de Beck; BPI: Inventário Breve de Dor; C&A: Camptocormia e Antecollis; DASS: Escala de Ansiedade e Estresse de Depressão; DEXA: Absortometria de Raio-X de Dupla Energia; DMS-III: Manual Diagnóstico e Estatístico de Transtornos Mentais; DP: Doença de Parkinson; END: Escala Numérica da Dor; ESS: Escala de sonolência de Epworth; EVA: Escala Visual Analógica; EVN: Escala Visual Numérica; FACS: Sistema de Codificação de Ação Facial; FOG-Q: Questionário de Congelamento da Marcha; HADS: Escala Hospitalar de Ansiedade e Depressão; HAMA: Escala de Classificação de Ansiedade de Hamilton; HAND: Escala de Classificação de Depressão de Hamilton; K-MMSE: Versão Coreana do Mini Exame do Estado Mental; K-PDQ-39: Versão Coreana do Questionário de Doença de Parkinson; KPPS: Escala King de Dor de Doença de Parkinson; LANSS: Avaliação de Leeds de Sintomas e Sinais Neuropáticos; LDP: Limiar de Dor por Pressão; LEED: Dose Equivalente de Levodopa. MA: Maior Depressão; MADRS: Escala de Avaliação de Depressão de Montgomery-Åsberg; MAIMS: Escala de Movimento Involuntário Anormal Modificado; MI: Menor Depressão; MMSE: Mini Exame do Estado Mental; MNSI: Instrumento de Triagem de Neuropatia de Michigan; MoCA: Avaliação Cognitiva de Montreal Versão Pequim; NFR: Reflexo de Flexão Nociceptiva; NHP: Perfil de Saúde de Nottingham; NMSQT: Questionário de Sintomas Não-Motores; NMSS: Escala de Sintomas Não-Motores; NO: Sem Depressão; NWDS: Escala de Deficiência de Northwestrn; OA: Osteoartrite; ODI: Indice de Incapacidade de Oswestry; PACA: Avaliação de Cuidados Paliativos; PANAS: Cronograma de Afeto Positivo e Negativo; PDI: Indice de Incapacidade de Dor; PDQ-39: Questionário de Doença de Parkinson; PDQ-8: Questionário da Doença de Parkinson com oito dimensões; PDSS: Escala de sono da doença de Parkinson; PDYS-26: Escala de Discinesia de Doença de Parkinson de 26 itens; PFS-16: Escala de Fadiga de Doença de Parkinson; PS: Síndrome de Pisa; PSE: Exame do Presente Estado; PSQI: Índice de Qualidade do Sono de Pittsburg; Limiar de Dor de Calor; QVRS: Qualidade de Vida Relacionada a Saúde; RMF: Ressonância Magnética Funcional; SF-36: Estudo de Resultados Médicos 36—Formulário Resumido do Item; SFMPQ: Questionário de Dor de McGill-Forma Curta; SMs: Sintomas Motores; SNMs: Sintomas Não-Motores; SPI: Síndrome das Pernas Inquietas; SQ: Questionário do Sono; TUG: Teste Timed UP and Go; UPDRS: Escala Unificada de Avaliação da Doença de Parkinson; WAIS-

III: Escala Wechsler de Inteligência para Adultos; WMS-III: Escala de Memória Wechsler; WOQ-9: Questionário de Desgaste-9; WS: Sensação de Calor:

Um total de 30.219 pessoas participaram dos estudos incluídos, sendo 24.593 pessoas com DP e 5.626 controles. Dentre os controles, foram incluídos os cônjuges e cuidadores (OZTURK; KOCER, 2018), pessoas com osteoartrite (RANA et al., 2018a), pós acidente vascular encefálico (BROETZ et al., 2007), doenças neuromusculares (GALAZKY et al., 2018), e pessoas com câncer, dor crônica ou diabetes, mas sem diagnóstico de doença neurológica de base (MCNAMARA et al., 2010), e voluntários saudáveis pareados por idade e gênero (ADEWUSI et al., 2018; CRUZ-ALMEIDA et al., 2020; DEFAZIO et al., 2008; EHRT; LARSEN; AARSLAND, 2009; JOSEPH et al., 2019; KUBO et al., 2016; LIEN et al., 2017; MAO et al., 2015; MYLIUS et al., 2011; NAISBY et al., 2021; POLIDORIO; LOTH; CARRILHO, 2009; POLLI et al., 2016; PRIEBE et al., 2015; RANA et al., 2013a, 2013b, 2014a, 2014b, 2016a, 2016b, 2016c, 2017, 2018a, 2018b, 2018c, 2019; TEKIN et al., 2015; WALMSLEY et al., 2020). O tamanho da amostra variou de 11 a 4.086 participantes com DP e de 11 a 1.960 controles.

Na tabela 2 estão descritos todos os intrumentos utilizados em cada estudo para avaliar os participantes. Foram utilizados 30 instrumentos validados diferentes para avaliar a dor dos participantes, a saber: Análise da avaliação da dor; Avaliação de Leeds de Sintomas e Sinais Neuropáticos (LANSS); Classificação de Ford; Diário de dor; Escala de Sintomas Não Motores (NMSS); Escala King's de Dor em doença de Parkinson (KPPS); Escala Likert de pontos; Escala Numérica da Dor (END) ou Escala de Classificação Numérica (ECN); Escala Visual Analógica (EVA); *Facial Action Coding System* (FACS); Índice de Incapacidade de Dor (PDI); Índice de incapacidade de Oswestry (ODI); Instrumento de Triagem de Neuropatia de Michigan; Inventário Breve de Dor (BPI); Inventário de Sensibilização Central; Limiar de dor elétrico; Limiar de dor por calor; *Pain Detect*; Questionário alemão da dor; Questionário de Desgaste de 9 sintomas (WOQ-9); Questionário de Dor de McGill (MPQ); Questionário de Sintomas Não-Motores para pacientes com DP (NMSQuest); Questionário King's de dor em doença de Parkinson; Questionário Pain O-meter; Somação temporal da dor por calor; e por fim, o recorte do domínio dor dos questionários de qualidade de vida EQ-5D, Parkinson Disease Questionnaire–39 (PDQ-39), Short-Form (SF-12v2) e Short Form-36 (SF-36), e a questão 1.9 da Escala de Avaliação da Doença de Parkinson Unificada da Sociedade de Distúrbios do Movimento Parte I (MDS-UPDRS-I).

Além desses instrumentos validados, os participantes também foram avaliados por meio de entrevista quanto a localização, fatores de alívio e de agravamento,

início do sintoma dor, se este sintoma foi antes ou depois do diagnóstico de DP, horário de maior e menor intensidade, e interferência nas atividades de vida diária (AVDs).

Dentre as 24.593 pessoas com DP que participaram dos estudos selecionados, 18.988 (77,20%) relataram dor dentre os SNMs. Apenas 16 estudos definiram a cronologia da dor como dor aguda ou crônica (BUHMANN et al., 2017; CHOI et al., 2017a, 2017b; DEFAZIO et al., 2008; FACCIO et al., 2020; FU et al., 2018; GALAZKY et al., 2018; GUNDOGDU et al., 2016a; MYLIUS et al., 2011; OZTURK et al., 2017a; OZTURK; KOCER, 2018; POLLI et al., 2016; SILVEIRA BAREZANI et al., 2020; SKOGAR et al., 2012; TEKIN et al., 2015; ZELLA et al., 2018), somente um descreveu a origem da dor como primária ou secundária (SUNG; KANG, 2022), e cinco artigos apresentaram o tipo de mecanismo de dor de acordo com a IASP (ADEWUSI et al., 2018; KINUGAWA et al., 2022; LEE et al., 2006; LIN et al., 2016; POLLI et al., 2016), além disso, houve grande divergência na terminologia utilizada para definir as características da dor nos critérios de inclusão e nos resultados encontrados, detalhes na tabela 3. Nos estudos, os autores definiram o tipo de mecanismo deste sintoma de acordo com o relato dos participantes, uma grande parte utilizou a escala de classificação de Ford ou o KPPS (CHAUDHURI et al., 2015; FORD, 2010), sendo assim, foi observada maior predominância de dor musculoesquelética em pessoas com DP (AGRAWAL et al., 2021; BEISKE et al., 2009; CHOI et al., 2017a, 2017b; DE MATTOS et al., 2019; DEFAZIO et al., 2017; FU et al., 2018; GHOSH et al., 2020; HIRSI et al., 2019; LI et al., 2022; LIEN et al., 2017; LIGUORI et al., 2021; LIN et al., 2016; MAO et al., 2015; MARTINEZ-MARTIN et al., 2019; NGUY et al., 2020; OZTURK et al., 2017b; PAUL et al., 2014; PRIEBE et al., 2015; RODRÍGUEZ-VIOLANTE et al., 2017; SAMANCI et al., 2022; SILVEIRA BAREZANI et al., 2020; SUNG; KANG, 2022; TINAZZI et al., 2006; VALKOVIC et al., 2015b; VILA-CHÃ et al., 2019b; ZELLA et al., 2018). Kobylecki et al., (2020) observaram que, na amostra de 1909 participantes, 76,6% tinham dor do tipo nociceptiva e 8,3% do tipo neuropática. Broetz et al. (2007) e Silverdale et al. (2018) identificaram que 38% (n total = 101) e 34% (n total = 1957) dos seus participantes, respectivamente, também apresentavam dor neuropática. Kinugawa et al. (2022) também observaram este tipo de dor nos participantes, mas apresentaram os dados em intensidade, mostrando que, no período *off*, a intensidade da dor neuropática é maior do que no período *on*. Adewusi et al. (2018) também investigaram a presença da dor do tipo neuropática e perceberam prevalência de 35,3% (n total = 51) dentre os participantes

com DP. Além disso, identificaram presença de alodinia, hiperalgesia e dor em queimação em 3, 7 e 11 participantes, respectivamente.

Tabela 3 – Critérios de dor apresentados dos estudos

Autor, data	Cronologia da dor		Origem da dor		Tipo de mecanismo de dor			Terminologia relatada nos critérios de inclusão	Terminologia relatada nos resultados
	Aguda	Crônica	Primária	Secundária	Neuropática	Nociceptiva	Nociplástica		
Indo, et al., 1983	NR	NR	NR	NR	NR	NR	NR	NR	NR
Starkstein et al., 1991	NR	NR	NR	NR	NR	NR	NR	NR	NR
Djaldetti et al., 2004	NR	NR	NR	NR	NR	NR	NR	NR	NR
Quittenbaum & Grahn, 2004	NR	NR	NR	NR	NR	NR	NR	NR	NR
Giuffrida et al., 2005	NR	NR	NR	NR	NR	NR	NR	NR	As dores foram qualificadas como dores osteoligamentar (reumatológica), muscular, neurogênica, dores de cabeça, visceral, síndrome sem pernas repouso, acatisia ou varia. Tambem foi utilizada a classificação de Wall e Melzack (1984).
Lee et al., 2006	NR	NR	NR	NR	X	X	NR	NR	a) Dor neuropática ou nociceptiva b) Uma nova classificação geral da dor

									baseada em um modelo utilizado no tratamento do câncer: dor relacionada à DPI; dor relacionada ao tratamento da DPI (ou seja, drogas da DPI que causam dor); Dor indiretamente relacionada à DPI (por exemplo, úlceras de pressão/ lesão por quedas); Dor não relacionada à DPI; Outras/múltiplas causas
Tinazzi et al., 2006	NR	NR	NR	NR	NR	NR	NR	NR	Classificação de Ford
Broetz et al., 2007	NR	NR	NR	NR	NR	NR	NR	NR	Dor radicular: projeção de dor na perna, dormência ou fraqueza na região onde a dor se projetou
Defazio et al., 2008	NR	X	NR	NR	NR	NR	NR	NR	Informações sobre qualquer dor presente no momento do estudo e com duração de pelo menos 3 meses foram registradas. A dor associada à disto-

									nia visível foi definida como dor distônica, enquanto a dor não distônica foi classificada como cólica (dor muscular), artrálgica (rigidez após repouso e dor ao movimento, confinada às articulações), neuropática periférica (dor no território de uma raiz ou nervo) e dor neuropática central (queimação ou formigamento)
Silva, et al., 2008	NR	NR	NR	NR	NR	NR	NR	NR	Classificação de Ford
Beiske et al., 2009	NR	NR	NR	NR	NR	NR	NR	NR	Caracterizou as qualidades da dor (ardente, maçante, dolorida, tensão, aperto ou irradiação), o início da dor (rastejante ou aguda) e sua flutuação, localização e fatores precipitantes/alívios. Com base nessas infor-

									mações e no exame clínico, cada dor relatada foi categorizada como dor musculoesquelética, dor radicular/neuropática, dor distônica ou CNP.
Ehrt et al., 2009	NR	NR	NR	NR	NR	NR	NR	NR	NR
Polidorio et al., 2009	NR	NR	NR	NR	NR	NR	NR	NR	NR
Roh et al., 2009	NR	NR	NR	NR	NR	NR	NR	NR	NR
McNamara et al., 2010	NR	NR	NR	NR	NR	NR	NR	NR	NR
Müller, et al., 2011	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mylius et al., 2011	X	X	NR	NR	NR	NR	NR	No grupo de pacientes com DP foi permitida apenas a dor clínica relacionada à DP	A dor aguda e crônica relacionada à DP foi avaliada por um pequeno questionário e classificada em 5 formas de acordo com Ford
Skogar et al., 2012	NR	X	NR	NR	NR	NR	NR	A dor crônica foi definida como a ocorrência de dor relacionada à DP por três dias ou mais por	NR

								semana durante pelo menos três meses imediatamente anteriores à inclusão no estudo	
Rana et al., 2013[1]	NR	NR	NR	NR	NR	NR	NR	NR	Classificação de Ford
Rana et al., 2013[2]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Coriolano et al., 2014	NR	NR	NR	NR	NR	NR	NR	Apenas se relatasse dor	NR
Rana et al., 2014	NR	NR	NR	NR	NR	NR	NR	NR	Dor não localizada; Dor distônica; Dor neuropática; Dor acatesica; Constante
Paul et al., 2014	NR	NR	NR	NR	NR	NR	NR	NR	Classificação de Ford
Mao et al., 2015	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ohara et al., 2015	NR	NR	NR	NR	NR	NR	NR	Pacientes com queixa de dor nas costas foram incluídos no estudo, a menos que as etiologias da dor não fossem aparentes.	NR
Priebe et al., 2015	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tekin., 2015	X	X	NR	NR	NR	NR	NR	Lesões passadas e dores que persistiram ≥ dois meses foram	NR

								definidas como crônicas.	
Valkovic et al., 2015	NR	NR	NR	NR	NR	NR	NR	NR	Classificação de Ford
Allen et al., 2016	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gundogdu et al., 2016	X	X	NR	NR	NR	NR	NR	Classificação de Ford	NR
Kubo et al., 2016	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lin et al., 2016	NR	NR	NR	NR	X	NR	NR	NR	Dor neuropática; Dor esquelética; neuralgia da raiz nervosa; dor de distonia; dor central; acatisia
Polli et al., 2016	NR	X	NR	NR	X	NR	NR	No grupo DP-dor, incluímos apenas pacientes que apresentavam dor persistente por mais de 3 meses e dor recorrente ou diária (item 2 da KPPS >2).	LANSS e KPPS
Rana et al., 2016[1]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rana et al., 2016[2]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rana et al., 2016[3]	NR	NR	NR	NR	NR	NR	NR	NR	Características de dor do BPI

Rodríguez-Violante et al., 2016	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Buhmann et al., 2017	X	X	NR	NR	NR	NR	NR	NR	NR
Choi et al., 2017[1]	N	X	NR	NR	NR	NR	NR	Dor persistente > 3 meses	Classificação de Ford
Choi et al, 2017[2]	N	X	NR	NR	NR	NR	NR	Dor persistente > 3 meses	Classificação de Ford
Defazio et al., 2017	NR	NR	NR	NR	NR	NR	NR	NR	Classificação de Ford
Lien et al., 2017	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ozturk et al., 2017	N	X	NR	NR	NR	NR	NR	Dor persistente > 3 meses	Classificação de Ford
Rana et al., 2017	NR	NR	NR	NR	NR	NR	NR	NR	NR
Adewusi et al., 2018	NR	NR	NR	NR	X	NR	NR	NR	Instrumento de Triagem de Neuropatia de Michigan e KPPS
Fu et al., 2018	N	X	NR	NR	NR	NR	NR	Dor persistente > 3 meses	Classificação de Ford
Galazky et al., 2018	X	X	NR	NR	NR	NR	NR	NR	NR
Ozturk & Kocer 2018	N	X	NR	NR	NR	NR	NR	Dor persistente > 3 meses	NR
Rana et al., 2018[1]	NR	NR	NR	NR	NR	NR	NR	NR	Características de dor do BPI
Rana et al., 2018[2]	NR	NR	NR	NR	NR	NR	NR	NR	Características de dor do BPI

Rana et al., 2018[3]	NR	NR	NR	NR	NR	NR	NR	NR	Características de dor do BPI
Scalzo et al., 2018	NR	NR	NR	NR	NR	NR	NR	NR	NR
Silva et al., 2018	NR	NR	NR	NR	NR	NR	NR	NR	NR
Silverdale et al., 2018	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Suzuki et al., 2018	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zella et al., 2018	NR	X	NR	NR	NR	NR	NR	Dor persistente > 12 semanas	NR
Alwardat et al., 2019[1]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alwardat et al., 2019[2]	NR	NR	NR	NR	NR	NR	NR	NR	NR
De Mattos et al., 2019	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Hirsi et al., 2019	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Joseph et al., 2019	NR	NR	NR	NR	NR	NR	NR	NR	NR
Martinez-Martin et al., 2019	NR	NR	NR	NR	NR	NR	NR	Declarou dores inexplicáveis no item 10 do NMSQ	KPPS
Rana et al., 2019	NR	NR	NR	NR	NR	NR	NR	NR	Características de dor do BPI
Vila-Chã et al., 2019[1]	NR	NR	NR	NR	NR	NR	NR	NR	Classificação de Ford

Vila-Chã et al., 2019[2]	NR	NR	NR	NR	NR	NR	NR	NR	Classificação de Ford
Cruz-Almeida et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Faccio et al., 2020	X	X	NR	NR	NR	NR	NR	NR	NR
Florin et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Geroin et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ghosh et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Gonçalves et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kobylecki et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	KPPS e LANSS
Nguy, 2020	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Rocha-Filho & Souza-Lima, 2020	NR	NR	NR	NR	NR	NR	NR	NR	As cefaleias foram classificadas de acordo com os critérios diagnósticos estabelecidos pela terceira edição da Classificação Internacional de Cefaleias (ICHD-3 beta)
Silveira Barezania et al., 2020	N	X	NR	NR	NR	NR	NR	Dor persistente > 3 meses	NR

Sung et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Walmsley et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yilmaz et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Agrawal et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Kinugawa et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kurihara et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Liguori et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Lopes et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Naisby, et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
O'Neill et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	KPPS e LANSS
Paul et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Prell et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Vila-Chã et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	Classificação de Ford
Gao et al., 2022	NR	NR	NR	NR	NR	NR	NR	Pessoa com DP relatando dor	NR
Gültekin et al., 2022	NR	NR	NR	NR	NR	NR	NR	NR	NR

Kinugawa et al., 2022	NR	NR	NR	NR	X	NR	NR	NR	NR
Li et al., 2022	NR	NR	NR	NR	NR	NR	NR	NR	Classificação de Ford
Samanci co., 2022	NR	NR	NR	NR	NR	NR	NR	NR	Classificação de Ford
Sung & Kang, 2022	NR	NR	X	NR	NR	NR	NR	NR	Classificação de Ford

NR: Não Relatado; X: utilizou o critério.

A intensidade de dor relatada pelos participantes, medida por meio da escala numérica de 11 pontos ou da escala visual analógica, foi de moderada a intensa, ou seja, > 4,07 de 10 (BROETZ et al., 2007; DEFAZIO et al., 2008; DJALDETTI et al., 2004; FU et al., 2018; GALAZKY et al., 2018; GONÇALVES et al., 2020; GÜLTEKIN et al., 2022; GUNDOGDU et al., 2016b; KUBO et al., 2016; LI et al., 2022; MAO et al., 2015; MÜLLER; MUHLACK; WOITALLA, 2011; MYLIUS et al., 2011; OZTURK; KOCER, 2018; POLLI et al., 2016; PRELL et al., 2021; RANA et al., 2013a; ROH et al., 2009; SCALZO et al., 2018; SILVA; CARVALHO, 2019; TINAZZI et al., 2006; YILMAZ et al., 2020). No entanto, também houve estudos que observaram a intensidade de dor leve entre 2,4 e 3,89 de 10 pontos (BEISKE et al., 2009; BUHMANN et al., 2017; CHOI et al., 2017a, 2017b; GAO et al., 2022a; KINUGAWA et al., 2022; KINUGAWA; MANO; SUGIE, 2021; LEE et al., 2006; LIN et al., 2016; MARTINEZ-MARTIN et al., 2019; VALKOVIC et al., 2015c). Quittenbaum & Grahn, (2004) identificaram a intensidade de dor máxima como moderada (5,1 de 10 pontos) e a mínima como leve (2,2 de 10 pontos). Lopes et al., (2021) identificaram que a média de intensidade de dor foi considerada leve nos pacientes tratados com a medicação antiparkinsoniana (2,17±0,39) do que pacientes não medicados (4,2±0,59). Gundogdu et al, (2016) descreveram que pessoas com DP tem a intensidade de dor do tipo musculoesquelética maior que os controles pareados por idade e gênero, não traz de forma quantitativa, mas informa que essa diferença não foi significativa, sendo assim houve viés de reportação. De Mattos et al, (2019) identificaram intensidade de dor de leve a moderada, porém também não descreveram os dados de forma quantitativa. Skogar et al, (2012) trazem os resultados da intensidade de dor em mediana (5,0 de 10 pontos), sendo assim não foi possível determinar o nível da intensidade de dor dos participantes incluídos. Suzuki et al, (2018) identificaram que 55,9% (n total de 159) das pessoas com DP e cefaleia, e 42,8% (n total de 42) das pessoas com DP e migrânea também tem intensidade de dor moderada a intensa. Alguns estudos descreveram a utilização dos instrumentos citados acima, mas não descreveram os dados quantitativos e/ou qualitativos nos resultados (DEFAZIO et al., 2017; GEROIN et al., 2020; NGUY et al., 2020; SILVERDALE et al., 2018b; VALKOVIC et al., 2015b).

A região das costas e/ou lombar foi o local de dor mais citado dentre os participantes dos estudos selecionados (ALWARDAT et al., 2019a; BROETZ et al., 2007; BUHMANN et al., 2017; CORIOLANO et al., 2014; GALAZKY et al., 2018; GEROIN et al., 2020; GONÇALVES et al., 2020; GÜLTEKIN et al., 2022; GUNDOGDU et al., 2016a; KINUGAWA; MANO; SUGIE, 2021; KUBO et al., 2016;

LIEN et al., 2017; OZTURK; KOCER, 2018; QUITTENBAUM; GRAHN, 2004b; ROH et al., 2009; SILVEIRA BAREZANI et al., 2020; SUNG; KANG, 2022; TINAZZI et al., 2006; VALKOVIC et al., 2015b; ZELLA et al., 2018). Outras regiões também foram citadas, tais como cabeça e pescoço (ALWARDAT et al., 2019b; FACCIO et al., 2020; INDO; NAITO; SOBUE, 1983; O'NEILL et al., 2021; SAMPAIO ROCHA-FILHO; LEITE SOUZA-LIMA, 2020; SILVA et al., 2018; SUZUKI et al., 2018), membros inferiores (DEFAZIO et al., 2008, 2017; LI et al., 2022; OHARA et al., 2015; PAUL et al., 2014; SCALZO et al., 2018; YILMAZ et al., 2020) e superiores (DE MATTOS et al., 2019; FU et al., 2018; SAMANCI et al., 2022; WALMSLEY et al., 2020). Martinez-Martin et al. (2019) observaram que 50,2% (n total = 300) dos seus participantes sentiam dor nos membros superiores e inferiores durante o sono. Skogar et al. (2012) identificaram que mais de 30% (n total = 28) das mulheres com DP sentem dor nos MMSS e de 21% a 30% (n total = 16) dos homens sentem dor nos membros inferiores (MMII). Vale ressaltar que alguns dos estudos citados já tinha como objetivo de estudo investigar uma única região de dor em específico.

Alguns estudos identificaram que de 5,5% a 53% de seus participantes mostraram que a dor surgiu antes do diagnóstico de DP (BUHMANN et al., 2017; GIUFFRIDA et al., 2005; SCALZO et al., 2018; SILVA; VIANA; QUAGLIATO, 2008; SKOGAR et al., 2012; VILA-CHÃ et al., 2019b; WALMSLEY et al., 2020). Também foi observado agravamento da dor com a progressão da doença (MYLIUS et al., 2011; RODRÍGUEZ-VIOLANTE et al., 2017; SILVEIRA BAREZANI et al., 2020; VALKOVIC et al., 2015b). No entanto, Lin et al. (2016) e Polli et al. (2016) observaram que, quanto mais jovem for a pessoa e/ou menor a duração da doença, maior a intensidade de dor. Nguy et al. (2020) descreveram que o aumento do tempo da doença está associado ao agravamento da dor musculoesquelética e a dor noturna.

Pacientes durante o momento *off* ou nos momentos de flutuação apresentaram maior intensidade de dor (FU et al., 2018; GIUFFRIDA et al., 2005; MAO et al., 2015; OZTURK; ÜNKAZAN, 2016; PRIEBE et al., 2015; SILVA et al., 2008; SILVERDALE et al., 2018b; STARKSTEIN; PREZIOSI; ROBINSON, 1991; TINAZZI et al., 2006). Sendo assim, foi observado que o tratamento farmacológico com a terapia antiparkinsoniana, antiinflamatórios não esteroidais, analgésicos, opioides e neurolépticos podem aliviar a dor em pessoas com DP (GHOSH et al., 2020; HIRSI et al., 2019; MÜLLER; MUHLACK; WOITALLA, 2011; RODRÍGUEZ-VIOLANTE et al., 2017; SKOGAR et al., 2012; VILA-CHÃ et al., 2019b).

Outros estudos (RANA et al., 2013a, 2013b, 2014b, 2016a, 2016b, 2016c, 2017, 2018a, 2018b, 2018c, 2019) identificaram: dor do tipo distônica como a mais prevalente; pessoas com DP tiveram maior frequência para descrever a dor como exaustiva, cansativa, penetrante e miserável; maior propensão a sentir dor nos MMII e MMSS; pessoas de origem caucasiana com DP tem maior probabilidade de sentir dor que pessoas de origem indiana com DP; pessoas com DP e osteoartrite tendem a relatar a dor como mais intensa e irradiada; quando solteiras, as pessoas com DP tem maior intensidade e interferência da dor em suas atividades que as casadas.

Quanto à qualidade metodológica dos 28 estudos incluídos do tipo caso-controle, em todos foram detectadas falhas metodológicas, sendo caracterizados entre moderada a baixa qualidade. As principais falhas detectadas foram: ausência do cálculo do tamanho da amostra; falta de seleção aleatória dos participantes do estudo; não uso de controles simultâneos; avaliação da exposição antes da medição do resultado; e ocultação dos avaliadores. Para este tipo de estudo, a ferramenta de avaliação da qualidade metodológica utilizada avalia a possibilidade de 12 falhas metodológicas, contudo, apenas 11 estudos dos 28 incluídos que tiveram um número inferior a seis falhas detectadas, ou seja, menos de 50% de falhas (EHRT; LARSEN; AARSLAND, 2009; LIN et al., 2016; QUITTENBAUM; GRAHN, 2004a; RANA et al., 2013b, 2016a, 2016b, 2016c, 2017, 2018b, 2018c, 2019), o menor número de falhas detectadas em um mesmo estudo foram quatro (RANA et al., 2019), detalhes na figura 2.

Avaliação de qualidade de estudos de caso-controle

Autor, data	Critérios											
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
Djaldetti et al., 2004	Y	N	N	NR	N	N	NA	N	N	Y	Y	N
Quittenbaum & Grahn, 2004	Y	Y	N	Y	Y	Y	NA	N	N	Y	NR	Y
Broetz et al., 2007	Y	Y	N	Y	N	Y	NA	N	N	N	NR	N
Defazio et al., 2008	Y	Y	N	Y	N	Y	NA	N	N	Y	NR	Y
Ehrt et al., 2009	Y	Y	N	Y	Y	Y	NA	N	N	Y	NR	Y
McNamara et al., 2010	Y	N	N	Y	Y	Y	NA	N	N	Y	NR	N
Mylius et al., 2011	Y	N	N	NR	N	Y	NA	NR	N	Y	NR	N
Rana et al., 2013	Y	Y	N	Y	Y	Y	NA	N	N	Y	NR	Y
Rana et al., 2014	Y	Y	N	Y	N	N	NA	N	N	Y	NR	Y
Mao et al., 2015	Y	N	N	Y	Y	Y	NA	N	N	Y	NR	Y
Priebe et al., 2015	Y	N	N	Y	Y	Y	NA	N	N	Y	NR	N
Tekin., 2015	Y	Y	N	Y	Y	Y	NA	N	N	N	Y	N
Gundogdu et al., 2016	Y	Y	N	NR	N	Y	NA	N	N	Y	NR	Y
Kubo et al., 2016	Y	N	N	N	N	Y	NA	N	N	Y	NR	N
Lin et al., 2016	Y	Y	N	Y	Y	Y	NA	NR	N	Y	NR	Y
Polli et al., 2016	Y	Y	N	Y	Y	Y	NA	N	N	Y	NR	N
Rana et al., 2016[1]	Y	Y	N	Y	Y	Y	NA	N	N	Y	NR	Y
Rana et al., 2016[2]	Y	Y	N	Y	Y	Y	NA	N	N	Y	NR	Y
Rana et al., 2016[3]	Y	Y	N	Y	Y	Y	NA	N	N	Y	NR	Y
Rana et al., 2017	Y	Y	N	Y	Y	Y	NA	N	N	Y	NR	Y
Adewusi et al., 2018	Y	N	N	NR	N	N	NA	N	N	Y	NR	Y
Galazky et al., 2018	Y	N	N	Y	N	Y	NA	N	N	N	NR	N
Rana et al., 2018[1]	Y	Y	N	Y	Y	Y	NA	N	N	Y	NR	Y
Rana et al., 2018[2]	Y	Y	N	NR	Y	Y	NA	N	N	Y	NR	N
Rana et al., 2018[3]	Y	Y	N	Y	Y	Y	NA	N	N	Y	NR	Y
Suzuki et al., 2018	Y	Y	N	N	N	Y	NA	N	N	Y	NR	Y
Rana et al., 2019	Y	Y	Y	Y	NR	Y	NA	NR	Y	Y	NR	Y
Gültekin et al., 2022	Y	Y	N	Y	Y	Y	NA	N	N	Y	NR	N

Baixo risco de viés Alto risco de viés Moderado risco de viés

Figura 2: Avaliação da qualidade metodológica dos artigos do tipo caso-controle, seguindo os 12 itens da avaliação de qualidade de estudos de caso-controle publicada pelo NHLBI. Y (sim), N (não) ou NR (não relatado), NA (não apliçável).

Em relação à qualidade metodológica dos 66 estudos incluídos do tipo coorte e transversal, foram encontradas falhas metodológicas em todos os estudos e, também, podem ser considerados como moderada a baixa qualidade. As mais frequentes falhas detectadas foram porcentagem de inclusão dos participantes elegíveis superior a 50%, ausência de cálculo do tamanho da amostra, avaliação da exposição antes da medição do resultado, prazo suficiente para ver um efeito, repetição da avaliação de exposição, ocultação dos avaliadores de resultados e perda de seguimento inferior a 20%. Para os estudos do tipo coorte e transversais, esta ferramenta avalia a possibilidade de 14 falhas metodológicas e apenas oito dos 66 estudos incluídos tiveram menos de sete falhas detectadas, ou seja, menos de 50% de falhas (FACCIO et al., 2020; GAO et al., 2022b; KURIHARA et al., 2021; LOPES et al., 2021; OZTURK; KOCER, 2018; PAUL et al.,

2021; ROH et al., 2009; SUNG et al., 2020), somente três estudos obtiveram o menor número de falhas detectadas em um mesmo estudo (FACCIO et al., 2020; KURIHARA et al., 2021; SUNG et al., 2020) que foram cinco, na figura 3.

Ferramenta de avaliação de qualidade para coorte observacional e estudos transversais

Autor, data	Critérios													
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.
Indo, et al., 1983	Y	N	NR	Y	N	N	N	Y	N	NA	N	NR	NR	NR
Starkstein et al., 1991	Y	N	NR	Y	N	N	N	Y	Y	NA	Y	Y	NR	Y
Giuffrida et al., 2005	Y	Y	NR	Y	N	N	N	Y	N	NA	N	NR	NR	N
Lee et al., 2006	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Tinazzi et al., 2006	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Silva, et al., 2008	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	N
Beiske et al., 2009	Y	N	N	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Polidorio et al., 2009	Y	N	NR	Y	N	N	N	N	N	NA	Y	NR	NR	N
Roh et al., 2009	Y	Y	Y	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Müller, et al., 2011	Y	N	N	NR	N	N	N	NA	N	NA	N	NR	NR	N
Skogar et al., 2012	Y	N	NR	Y	N	N	N	Y	Y	NA	N	NR	NR	Y
Rana et al., 2013	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Coriolano et al., 2014	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	N
Paul et al 2014	Y	Y	N	Y	N	N	N	Y	Y	NA	Y	NR	NR	N
Ohara et al., 2015	Y	N	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	N
Valkovic et al., 2015	Y	N	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	N
Allen et al., 2016	Y	N	NR	Y	N	N	N	Y	N	NA	N	NR	NR	Y
Rodríguez-Violante et al., 2016	Y	N	N	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Buhmann et al., 2017	Y	N	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	N
Choi et al., 2017[1]	Y	N	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Choi et al, 2017[2]	Y	N	Y	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Defazio et al., 2017	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Lien et al., 2017	Y	Y	N	Y	N	N	N	N	N	N	N	NR	NR	Y
Ozturk et al., 2017	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Fu et al., 2018	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Ozturk & Kocer 2018	Y	Y	Y	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Scalzo et al., 2018	Y	Y	N	Y	N	N	N	Y	Y	NA	Y	NR	NR	N
Silva et al., 2018	Y	Y	Y	Y	Y	N	N	Y	Y	NA	N	NR	NR	N
Silverdale et al., 2018	Y	N	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Zella et al., 2018	Y	N	NR	Y	N	N	N	N	N	NA	N	NR	NR	NR
Alwardat et al., 2019[1]	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	N
Alwardat et al., 2019[2]	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	N
De Mattos et al., 2019	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	N
Hirsi et al., 2019	Y	Y	NR	Y	N	N	N	N	Y	NA	Y	N	NR	Y
Joseph et al., 2019	Y	N	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Martinez-Martin et al., 2019	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Vila-Chã et al., 2019[1]	Y	N	Y	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Vila-Chã et al., 2019[2]	Y	N	Y	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Cruz-Almeida et al., 2020	Y	N	NR	Y	N	N	N	Y	Y	N	Y	N	NR	N
Florin et al., 2020	Y	N	NR	Y	N	N	N	Y	Y	N	Y	N	NR	N
Faccio et al., 2020	Y	Y	Y	Y	Y	N	NA	Y	Y	NA	Y	N	NR	Y
Geroin et al., 2020	Y	N	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Ghosh et al., 2020	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Gonçalves et al., 2020	Y	N	NR	Y	N	N	NA	Y	N	NA	N	N	NR	Y
Kobylecki et al., 2020	Y	N	NR	Y	N	N	N	Y	Y	N	Y	N	NR	Y
Nguy, 2020	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Rocha-Filho & Souza-Lima, 2020	Y	Y	NR	Y	N	N	N	Y	Y	NA	Y	N	NR	N
Silveira Barezania et al., 2020	Y	N	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	Y
Sung et al., 2020	Y	Y	NR	Y	N	Y	Y	Y	Y	NA	Y	N	NR	Y
Walmsley et al., 2020	Y	Y	N	Y	N	N	N	Y	N	NA	N	NR	NR	Y
Yilmaz et al., 2020	Y	N	NR	Y	N	N	N	Y	Y	NA	Y	NR	NR	N
Agrawal et al., 2021	Y	Y	NR	Y	N	N	N	Y	Y	N	Y	N	NR	Y
Kinugawa et al., 2021	Y	Y	NR	NR	N	N	NA	N	N	NA	Y	N	NR	Y
Kurihara et al., 2021	Y	Y	NR	Y	N	Y	Y	Y	Y	N	Y	N	NR	Y
Liguori et al., 2021	Y	Y	NR	Y	N	N	NA	Y	Y	NA	Y	N	NR	Y
Lopes et al., 2021	Y	Y	N	Y	N	N	Y	Y	Y	NA	Y	N	NR	Y
Naisby, et al., 2021	Y	Y	N	Y	N	N	N	Y	N	N	N	N	NR	N
O'Neill et al., 2021	Y	Y	NR	Y	N	N	NA	Y	Y	NA	Y	N	NR	Y
Paul et al., 2021	Y	Y	NR	Y	N	Y	Y	N	N	NA	Y	N	NR	Y
Prell et al., 2021	Y	Y	NR	Y	N	N	N	Y	Y	N	Y	N	NR	Y
Vila-Chã et al., 2021	Y	N	NR	N	N	N	NA	Y	Y	NA	Y	N	NR	NR
Gao et al., 2022	Y	Y	NR	Y	N	Y	NA	Y	Y	NA	Y	N	NR	Y
Kinugawa et al., 2022	Y	Y	NR	Y	N	N	N	Y	Y	N	Y	N	NR	N
Li et al., 2022	Y	Y	NR	Y	N	N	NA	Y	Y	NA	Y	N	NR	Y
Samanci et al., 2022	Y	N	NR	N	N	Y	Y	Y	N	N	N	N	N	N
Sung & Kang, 2022	Y	Y	NR	Y	N	N	N	Y	Y	N	Y	N	NR	N

Baixo risco de viés | Alto risco de viés | Moderado risco de viés

Figura 3: Avaliação da qualidade metodológica dos artigos do tipo observacional coorte e transversal seguindo os 14 itens da Avaliação de qualidade de estudos de coorte e transversal publicada pelo NHLBI. Y (sim), N (não) ou NR (não relatado), NA (não aplicável).

Apenas cinco dos 94 artigos avaliaram a dor das pessoas com DP de forma semelhante (RANA et al., 2016ª, 2016b, 2017, 2018b, 2018c) por meio do BPI, porém um desses cinco não avaliou a interferência da dor (RANA et al., 2016b). Os estudos mostraram que o grupo controle tende a sentir mais dor que o grupo DP tanto na interferência ($Tau^2 = 9.08$; $Chi^2 = 23.95$, df = 4 ($P < 0.0001$); $I^2 = 83\%$; Test for overall effect: $Z = 3.98$ $P < 0.0001$) quanto para a intensidade ($Tau^2 = 10.30$; $Chi^2 = 8.78$, df = 3 ($P = 0.03$); $I^2 = 66\%$; Test for overall effect: $Z = 5.01$ $P < 0.00001$). Detalhes na figura 4 e 5.

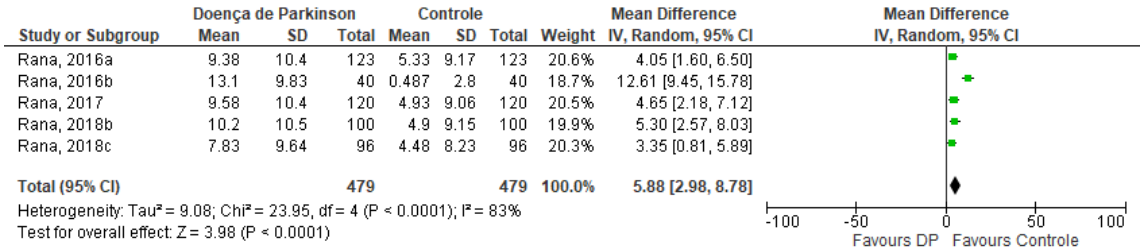

Figura 4: Forest plot do BPI – interferência de dor. A severidade da dor em comparação do grupo controle com o grupo DP utilizando o BPI.

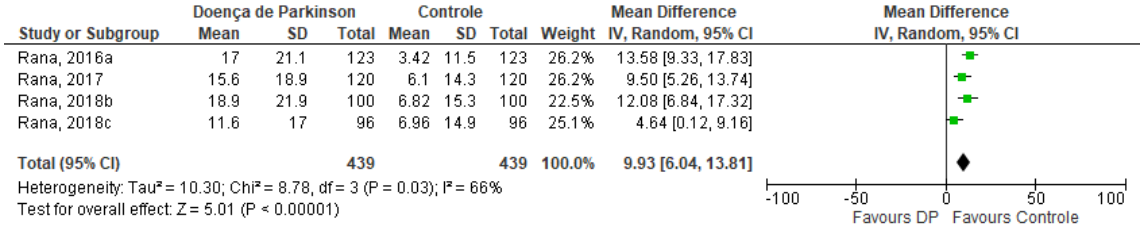

Figura 5: Forest plot do BPI – intensidade de dor. A intensidade da dor em comparação do grupo controle com o grupo DP utilizando o BPI.

Duas outras publicações (ADEWUSI et al., 2018; POLLI et al., 2016) relataram de forma similar a avaliação da dor em pessoas com DP através da KPPS. No entanto, os estudos incluídos na análise mostraram diferença na dor desta população em comparação com os controles ($Tau^2 = 3.35$; $Chi^2 = 23.55$, df = 1 ($P < 0.00001$); $I^2 = 96\%$; Test for overall effect: $Z = 1.50$ $P = 0.13$), figura 6.

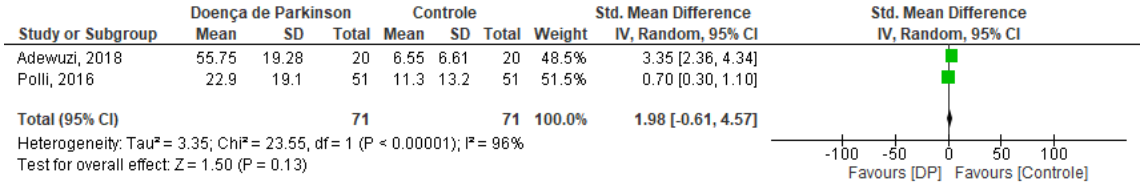

Figura 6: Forest plot da KPPS. Evidência da utilização da KPPS para avaliar a dor de pessoas com DP em comparação com grupo controle

Da mesma forma, outros dois estudos avaliaram a intensidade de dor das pessoas com DP com a EVA (DEFAZIO et al., 2008; OZTURK; KOCER, 2018), todavia, também foi observado que não há diferença entre os grupos para a avaliação desta característica (Tau² = 0.09; Chi² = 11.76, df = 1 (P = 0.0006); I² = 91%; Test for overall effect: Z = 0.77 P = 0.44). Detalhes na figura 7

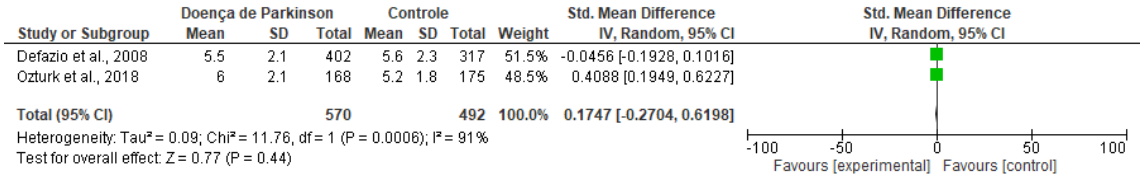

Figura 7: Forest plot da EVA. Evidência da utilização da EVA para avaliar a intensidade da dor de pessoas com DP em comparação com grupo controle

Procurando evitar a interferência de overlap levando em consideração que apenas os estudos de um mesmo autor possibilitaram a execução da meta análise (RANA et al., 2016a, 2016b, 2017, 2018b, 2018c) foi utilizado o efeito fixo para a análise de subgrupo do BPI apresentando os seguintes resultados para a interfência da dor (Tau² = 9.08; Chi² = 23.95, df = 4 (P < 0.0001); I² = 83%; Test for overall effect: Z = 3.98 (P < 0.0001)), intensidade de dor (Tau² = 10.30; Chi² = 8.78, df = 3 (P = 0.03); I² = 66%; Test for overall effect: Z = 5.01 (P < 0.00001)) e total (Tau² = 12.06; Chi² = 44.56, df = 8 (P < 0.00001); I² = 82%; Test for overall effect: Z = 5.73 (P < 0.00001); Test for subgroup differences: Chi² = 2.68, df = 1 (P = 0.10), I² = 62.7%). Sendo assim, podemos observar que há a evidencia de que a avaliação da intensidade de dor com o BPI pode retratar a dor de pessoas com DP, foi encontrada uma heterogeneidade de 66% para este subgrupo, porém em ambos subgrupos, o grupo controle apresentou maior dor em relação ao grupo DP como pode ser observado na figura 8.

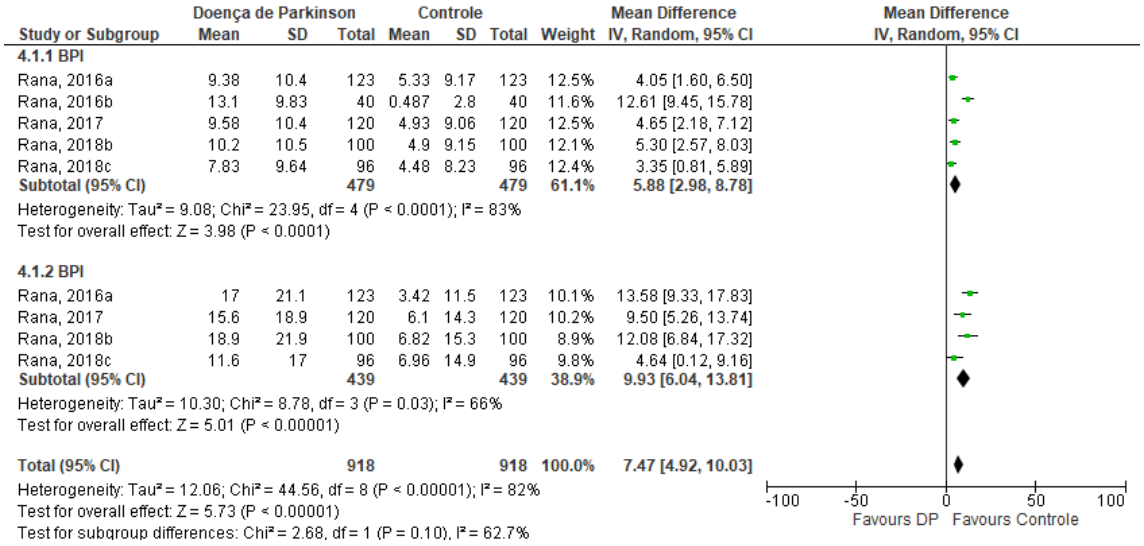

Figura 8: Forest plot da análise dos subgrupos do BPI. Evidências da interferência de dor, intensidade de dor e total, respectivamente.

6. DISCUSSÃO

Dentre os quase 15 mil artigos encontrados, foram selecionados 94, sendo que 28 do tipo caso controle e 66 do tipo coorte e transversal, dos quais englobaram uma análise de 24.593 pessoas com DP e 5.626 controles. Foram utilizados 30 diferentes instrumentos para a avaliação da dor em pessoas com DP, os mais utilizados foram EVA, END, BPI, KPPS e MPQ. As principais características da dor encontradas em pessoas com DP foram na maioria, dor do tipo musculoesquelética, com intensidade de moderada a intensa, majoritariamente na região das costas, que possivelmente é o sintoma inicial da DP e que tende a intensificar com o agravamento da doença e há alívio com a terapia farmacológica antiparkinsoniana.

No que diz respeito ao tipo de mecanismo da dor em pessoas com DP, vários dos estudos selecionados utilizaram definições como musculoesquelética, radicular, distônica, central ou primária, acatisia, crônica, relacionada a flutuação, noturna, orofacial ou descoloração e edema, de acordo com a Classificação de Ford e a KPPS (CHAUDHURI et al., 2015; FORD, 2010). Já a IASP, descreve que o tipo de mecanismo da dor pode ser definido como neuropática, nociceptiva e nociplástica (RAJA et al., 2020). Este sintoma também pode ser considerado como misto, a dor mista é definida pela presença dos componentes dos outros três tipos de dor (HIGASHIBATA et al., 2020). Dentre os estudos selecionados, apenas cinco seguiram a terminologia da IASP (ADEWUSI et al., 2018; BROETZ et al., 2007; KINUGAWA; MANO; SUGIE, 2021; KOBYLECKI et al., 2020; SILVERDALE et al., 2018b). Sendo assim, observamos que os dados seguem classificações inapropiadas e que não seguem os conceitos da IASP, impactando na inviabilização desses estudos como evidencias para elaboração de um plano de tratamento eficaz para as pessoas com DP.

Teoricamente, a dor em pessoas com DP poderia ser caracterizada como o tipo de dor mista, visto que elas têm o relato de dor em um tecido não neural, mas também pode haver uma lesão no sistema somatossensorial e, também, possuem a nocicepção alterada, ou seja, dor nociceptiva, neuropática e nociplástica, respectivamente. Portanto, seguindo os atuais conceitos da IASP, a dor em pessoas com DP pode ser do tipo mista e há a necessidade que novos estudos avaliem com instrumentos apropriados o tipo de mecanismo de dor desta população para que tenhamos evidência desta característica.

A dor pode ser avaliada em diversos momentos durante a anamnese da pessoa, sendo assim, ela pode ser quantificada em repouso, movimento, logo após uma atividade, pois diversos fatores podem influenciá-la (TALBOT et al., 2019). Dentre os 94 estudos incluídos, nenhum descreve o exato momento em que a dor das pessoas com DP foi avaliada. Diante dos desenhos metodológicos dos estudos selecionados, supõe que foi em repouso devido a ser realizado apenas uma única avaliação e não descrever detalhes condizentes de que possam ter acontecido durante o movimento. No entanto, se faz necessário controlar melhor todos os fatores que possam influenciar na dor em pessoas com DP para que seja possível caracterizá-la de maneira adequada.

Atualmente, diversos instrumentos já foram descritos como apropriados para avaliar a intensidade da dor como a EVA, END, BPI, MPQ, dentre outros (CARLSSON, 1983; CLEELAND; RYAN, 1994; MELZACK, 1975; RAKEL et al., 2012). Há a necessidade de utilizar o instrumento adequado para a avaliação da dor para que o resultado obtido seja fidedigno e coerente com o que foi proposto. Houve estudos que pretendiam determinar o desfecho intensidade de dor, porém utilizaram instrumentos que não são adequados ou usaram recortes de instrumentos destinados a outras variáveis ou até mesmo não validados (ALLEN et al., 2016; BEISKE et al., 2009; GALAZKY et al., 2018; GIUFFRIDA et al., 2005; GONÇALVES et al., 2020; INDO; NAITO; SOBUE, 1983; JOSEPH et al., 2019; KUBO et al., 2016; LIN et al., 2016; MCNAMARA et al., 2010; MYLIUS et al., 2011; NAISBY et al., 2021; PRELL et al., 2021; RANA et al., 2013a, 2014b; SAMPAIO ROCHA-FILHO; LEITE SOUZA-LIMA, 2020; SILVA; VIANA; QUAGLIATO, 2008; STARKSTEIN; PREZIOSI; ROBINSON, 1991; WALMSLEY et al., 2020; ZELLA et al., 2018), com isso não foi possível interpretar os dados desses estudos para a característica citada.

O maior índice de relato no que se refere à região de maior intensidade de dor foi a coluna lombar. Isso pode estar relacionado a um dos principais SMs que é a instabilidade postural, visto que ocorre a anteriorização do centro gravidade como forma de compensação, além disso pode estar associado a outros SM que como resultado irá diminuir o controle motor (SOUSA, 2021). Na dor lombar, podem existir diferentes mecanismos fisiopatológicos levando a quadros inflamatório-nociceptivos, neuropáticos ou disfuncionais centrais, sendo considerada como dor mista que envolve mecanismos tanto nociceptivos como neuropáticos (PICELLI et al., 2016).

A DP tem como características a marcha festinante que é a marcha em passos curtos e rápidos, e o *freezing of gate* que é a dificuldade em iniciar o movimento, dando a sensação de congelamento (FACTOR et al., 2014; TAKAKUSAKI, 2017). Estas características podem estar associadas à incidência de dor em membros inferiores, devido ao enrijecimento dos músculos e articulações, o que dificulta a realização dos movimentos e, também, pode gerar contraturas (WASEEM; GWINN-HARDY, 2001). Desta forma, é possível identificar que a dor nos membros inferiores das pessoas com DP pode ser do tipo nociceptiva.

Os SMs desta população tendem a causar alterações posturais, de equilíbrio e de marcha, o que impacta na diminuição do controle motor (SCHONEBURG et al., 2013). Além disso, a neurodegeneração periférica dos gânglios da base, ocasiona também esse déficit motor (CHASTAN; DECKER, 2019). Quando o indivíduo tem a experiência da dor ou tem o conhecimento de que a irá sentir, ele se movimenta de forma diferente, posturas e padrões de movimento que minimizem este sintoma, mesmo que momentaneamente (KANTAK; JOHNSON; ZARZYCKI, 2022). Sendo assim, as pessoas com DP têm uma grave diminuição do controle motor tanto pelo agravamento da doença, quanto pela persistência e aumento da intensidade da dor.

A IASP define a dor como uma experiência sensorial e emocional desagradável associada ou semelhante a uma lesão tecidual real ou potencial, e que pode estar relacionada a fatores biológicos (RAJA et al., 2020). Alguns estudos observaram que as pessoas com DP podem sentir a dor com um dos primeiros sintomas da doença (BUHMANN et al., 2017; GIUFFRIDA et al., 2005; SCALZO et al., 2018; SILVA; VIANA; QUAGLIATO, 2008; VILA-CHÃ et al., 2019a; WALMSLEY et al., 2020). Isso pode estar relacionado devido ao dano inicial da atrofia dos neurônios da substância negra e diminuição da produção de dopamina, juntamente com a manifestações iniciais dos SMs (WASNER; DEUSCHL, 2012).

Quando observado os relatos da intensidade, local, termos para descrever a dor e o agravamento com o avanço da doença, fica sugestivo o aumento da responsividade nociceptiva central e periférica, portanto, sensibilização central e periférica, impactando na diminuição do limiar de dor nessa população. Apenas um estudo dentre os incluídos avaliou a sensibilização central das pessoas com DP o qual corrobora que a dor desta população está relacionado a este sintoma (NGUY et al., 2020). No entanto, é necessário

que mais estudos investiguem melhor a associação entre essas variáveis em pessoas com DP.

Dentre os diversos instrumentos utilizados para avaliar as características da dor em pessoas com DP, só foi possível analisar de forma qualitativa três destes: BPI, KPPS e EVA. Entretanto, para a KPPS e EVA não houve evidência de haja diferença nas características da dor desta população em comparação com diferentes controles e também houve uma altíssima heterogeneidade entre os estudos o que reforça esta análise, além de que so foi possível realizar a meta-análise com apenas dois estudos para cada um dos instrumentos sendo que 15 publicações das 94 incluídas utilizaram a KPPS e 29 a EVA.

Com a análise do BPI observamos que há a evidência de que é um instrumento que é sensível para avaliar as características da dor em pessoas com DP, todavia o grupo controle apresentou maior intensidade e severidade de dor que a população alvo. Os estudos elegíveis para a realização da meta-análise com este instrumento foram do mesmo grupo de autores e da mesma amostra, variando apenas o número de participantes em cada publicação, supondo um provável *overlap* dos participantes. Com isso, não podemos afirmar se a evidência encontrada é fidedigna ou se o dado encontrado foi é impreciso por se tratar de uma mesma amostra analisada de forma repetida.

Quando analisado o subgrupo interferência da dor do BPI, foi encontrada alta heterogeneidade e que os controles apresentam maior interferência da dor em suas atividades que as pessoas com DP. No entanto, quando é avaliada esta característica deve ser ressaltado que ela está diretamente relacionada com o estado cognitivo do paciente, sendo que um dos SNMs da DP é o comprometimento cognitivo e isso acontece de forma semelhante com a EVA. Contudo, encontramos que tanto o subgrupo interferência da dor do BPI e a EVA o grupo controle relata maior interferência e intensidade de dor que pessoas com DP.

Já com o subgrupo intensidade de dor do BPI foi o único que houve a evidência positiva sobre esta característica da dor das pessoas com DP, principalmente por apresentar baixa heterogeneidade mesmo com o *overlap*, porém os controles utilizados apresentaram maior intensidade que as pessoas com DP. Este subgrupo tem semelhança com a END, que é um instrumento mais simples de ser utilizado para avaliar a intensidade da dor desta população, porém não foi possível realizar a meta-análise com os estudos que usou este instrumento. Sendo assim, é possível reforçar a hipótese de que

instrumentos mais complexos ou que exijam maior função cognitiva tem menor sensibilidade e precisão determinar as características da dor em pessoas com DP.

Há evidência de que a terapia farmacológica antiparkinsoniana pode ser um fator de alívio da dor devido à reposição dopaminérgica, sendo assim haverá o alívio dos SMs e diminuição de dor nociceptiva (WASEEM; GWINN-HARDY, 2001; WASNER; DEUSCHL, 2012). A prática da atividade física, principalmente o exercício aeróbico, pode amenizar os SMs e diminuir os sintomas dolorosos (AMBROSE; GOLIGHTLY, 2015a; WU; LEE; HUANG, 2017). Portanto, é necessário incentivar que as pessoas com DP sigam tanto o tratamento farmacológico quanto o não-farmacológico para que ambos possam aliviar os sintomas dolorosos, além dos SMs e dos outros SNMs, e consequentemente melhorar a qualidade de vida.

Em pessoas com dor crônica, o tratamento fisioterapêutico e a práticas de exercícios realizados de forma regular tem eficácia no alívio da dor. Este desfecho ocorre devido à atividade física regular diminuir a excitabilidade e melhora a inibição tanto no sistema nervoso central quanto no sistema imunológico (CHIMENTI; FREY-LAW; SLUKA, 2018). Devido à sensibilização central, a pessoa com DP tende a ter menor limiar de dor e com a prática regular de exercícios estes pacientes terão efeitos favoráveis na redução da gravidade da dor e melhora da função física, além de ser uma intervenção com poucos efeitos adversos.

Outra terapia com efeito analgésico que pode ser utilizada é a terapia multimodal que consiste no uso de intervenções terapêuticas diferentes e mecanismos de ação diferentes de forma simultânea visando o alívio da dor (RAJA et al., 2020). Tulder et al. (2000) trazem que este tipo de terapia tem efeito na redução da intensidade de dor em pessoas com dor lombar crônica. Além disso, ela também possui efeitos biopsicossociais, estimula o controle motor, melhora o equilíbrio e a marcha (SOUSA, 2021). Sendo assim, terapia multimodal em pessoas com DP pode minimizar os SMs e SNMs, incluindo o alívio da dor. Um outro fator da utilização este método terapêutico, é que com ele os pacientes tendem a utilizar menos fármacos analgésicos alternativos (HORN; KANESHIRO; TSUI, 2020).

Atualmente, ainda há a crença dos profissionais da saúde de que quando o paciente está sentindo dor, ele deve se manter em repouso e como a DP é uma doença crônica, essa teoria se torna ainda mais incisiva. No entanto, já há evidência que ao fazer

alguma atividade ou ao gerar movimentação, há um efeito analgésico (AMBROSE; GOLIGHTLY, 2015b). É dever dos profissionais da saúde conscientizarem os seus pacientes e realizar a educação em saúde sobre a dor e de que o repouso também pode causar e/ou intensificar dor e que estes devem procurar uma terapia do seu agrado para que possa minimizar os sintomas dolorosos.

Os fatores psicossociais como ansiedade, depressão, catastrofização, cinesiofobia, autoeficácia no manejo e enfrentamento relacionado à dor podem influenciar no relato dela (TALBOT et al., 2019). Quando o paciente apresenta estas condições, ele tem maior dificuldade em realizar os movimentos impactando na funcionalidade e qualidade de vida (EDWARDS et al., 2016). Sendo assim, há a necessidade da avaliação multidimensional nas pessoas com DP para que seja realizado a abordagem biopsicossocial, visto que os fatores biológicos podem influenciar nos psicossociais e vice-versa.

Os estudos incluídos tiveram várias limitações. Diversos estudos não utilizaram um grupo controle adequado quando avaliam pessoas com doenças neurológicas crônicas ou que afetam o movimento, ou até mesmo quando utilizam participantes que tem vínculo com a população alvo. A qualidade metodológica dos estudos foi baixa na maioria dos casos, apenas 18 dos 94 tiveram menos de 50% de falha metodológica. Somente três estudos calcularam o tamanho da amostra para o recrutamento dos participantes e, também, apenas três outros estudos realizaram o cegamento dos avaliadores. Vários estudos selecionados não utilizaram instrumentos adequados para a avaliação da dor. Alguns estudos descreveram a utilização de alguns instrumentos de avaliação, no entanto não apresentam os resultados dos mesmos. As limitações do presente neste estudo foi a dificuldade em obter os artigos na íntegra e não encontrar um padrão para avaliar a dor em pessoas com DP.

Como pontos fortes podemos ressaltar que esta revisão é a única que descreve as principais características da dor em pessoas com DP; este estudo traz diversas lacunas a serem avaliadas como o tipo de mecanismo de dor em pessoas com DP, a dor como um sintoma inicial da doença e as justificativas para as regiões de maior intensidade deste sintoma. Esta revisão também descreve que a qualidade metodológica dos estudos que avaliaram a dor em pessoas com DP que foi de moderada a baixa, mostrando que os próximos estudos necessitam de maior rigor metodológico para sua execução. Neste

estudo são descritos os principais instrumentos de avaliação que foram utilizados para a avaliação da dor em pessoas com DP e, principalmente, não há a padrão para caracterizar a dor destas pessoas.

Estudos futuros devem buscar compreender melhor o SNM dor em pessoas com DP, construir um método de avaliação adequado para este sintoma seguindo as terminologias da IASP para a definição do tipo de mecanismo de dor, utilizar instrumentos adequados que caracterize a dor, investigar os fatores de alívio e de agravamento deste sintoma, para que assim seja possível compreender melhor sobre a dor em pessoas com DP.

7. CONCLUSÕES

No presente estudo, foi possível observar que a maior parte das pessoas com DP sentem dor com intensidade moderada a grave, com tipo de mecanismo misto, principalmente na região lombar e que alivia com o tratamento farmacológico antiparkinsoniano, além de que a dor pode ser um dos primeiros sintomas e tem o agravamento com o avanço da doença.

Entretanto, foi observado que não há um padrão para caracterizar a dor em pessoas com DP, visto que é um sintoma presente na maioria desta população, mas não existem instrumentos suficientemente específicos e sensíveis para determinar e quantificar estas características em comparação a diferentes controles. Por estes motivos, é necessário que novos estudos sejam realizados para que seja possível realizar a caracterização da dor em pessoas com DP.

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APÊNDICE

The Journal of Pain

There is no reasonable standard for characterizing pain in patients with Parkinson's disease: a systematic review and meta-analysis

--Manuscript Draft--

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Corresponding Author:	Josimari Melo DeSantana, PhD Universidade Federal de Sergipe. Graduate Program in Health Science and Graduate Program in Physiological Science. Aracaju, Sergipe BRAZIL
First Author:	Josimari Melo DeSantana, PhD
Order of Authors:	Josimari Melo DeSantana, PhD
	Menezes, E.O.
	Dantas, M.I.O.
	Santos, A.O.
	DeSantana, J.M.
Abstract:	Parkinson's disease (PD) is a chronic and degenerative disease with both motor and non-motor symptoms. Pain is one of the main non-motor symptoms and its main characteristics are still unclear in patients with PD. The aim of this study was to characterize pain in people with PD and verify instruments that have been used to measure and classify pain. Cross-sectional, longitudinal, case-control and cohort observational studies assessing pain in the population with PD were included. Searches took place in nine databases to find articles that met the criteria of this study. The instrument used to assess the methodological quality of the included articles was the one published by the National Heart, Lung and Blood Institute (NHLBI). A total of 14,197 articles were found, of which 94 were selected (28 case-control and 66 cohort and cross-sectional type), including 24,593 people with PD and 5.626 controls. Thirty different instruments were used to assess pain in people with PD. Among the main characteristics of pain, it was found that most people with PD experience moderate to severe musculoskeletal pain, especially in the back region, which is possibly the initial symptom of PD and intensifies with the worsening of the disease. There is relief with antiparkinsonian drug therapy. In this review, it was observed that there is no pattern to characterize pain in people with PD, since it is a symptom present in the majority of this population, but there are not enough specific and sensitive instruments to determine and quantify these characteristics.
Suggested Reviewers:	

Cover Letter

There is no reasonable standard for characterizing pain in patients with Parkinson's disease:
a systematic review and meta-analysis

Menezes, E. O.[a], Dantas, M. I. O.[b], Santos, A. O.[b] & DeSantana, J. M.[a,b,c]

[a] Federal University of Sergipe, Graduate Program in Health Science, Sao Cristóvão-SE, Brazil

[b] Federal University of Sergipe, Graduate Program in Physiological Sciences, Sao Cristóvão-SE, Brazil

[c]Department of Physical Therapy, Federal University of Sergipe, Graduate Program in Physiological Sciences, Graduate Program in Health Science, São Cristóvão-SE, Brazil

Josimari M DeSantana, PhD, PT.

Laboratório de Pesquisa em Neurociência/LAPENE. Departamento de Fisioterapia. Universidade Federal de Sergipe. Av Marechal Rondon, s/n. Bairro Rosa ElzeCEP 49100-000. Aracaju, Sergipe, Brasil. josimelo@academico.ufs.br

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Menezes, E. O.[a], Dantas, M. I. O.[b], Santos, A. O.[b] & DeSantana, J. M.[a,b,c]

[a] Federal University of Sergipe, Graduate Program in Health Science, Sao Cristóvão-SE, Brazil

[b] Federal University of Sergipe, Graduate Program in Physiological Sciences, Sao Cristóvão-SE, Brazil

[c]Department of Physical Therapy, Federal University of Sergipe, Graduate Program in Physiological Sciences, Graduate Program in Health Science, São Cristóvão-SE, Brazil

Josimari M DeSantana, PhD, PT.

Laboratório de Pesquisa em Neurociência/LAPENE. Departamento de Fisioterapia. Universidade Federal de Sergipe. Av Marechal Rondon, s/n. Bairro Rosa ElzeCEP 49100-000. Aracaju, Sergipe, Brasil. josimelo@academico.ufs.br

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ABSTRACT

Parkinson's disease (PD) is a chronic and degenerative disease with both motor and non-motor symptoms. Pain is one of the main non-motor symptoms and its main characteristics are still unclear in patients with PD. The aim of this study was to characterize pain in people with PD and verify instruments that have been used to measure and classify pain. Cross-sectional, longitudinal, case-control and cohort observational studies assessing pain in the population with PD were included. Searches took place in nine databases to find articles that met the criteria of this study. The instrument used to assess the methodological quality of the included articles was the one published by the National Heart, Lung and Blood Institute (NHLBI). A total of 14,197 articles were found, of which 94 were selected (28 case-control and 66 cohort and cross-sectional type), including 24,593 people with PD and 5.626 controls. Thirty different instruments were used to assess pain in people with PD. Among the main characteristics of pain, it was found that most people with PD experience moderate to severe musculoskeletal pain, especially in the back region, which is possibly the initial symptom of PD and intensifies with the worsening of the disease. There is relief with antiparkinsonian drug therapy. In this review, it was observed that there is no pattern to characterize pain in people with PD, since it is a symptom present in the majority of this population, but there are not enough specific and sensitive instruments to determine and quantify these characteristics.

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Perspectives: This review is the only one that identifies that there is no standard to characterize this symptom and that there are not enough specific and sensitive instruments to determine and quantify it. This evidence could serve as a basis for new studies that seek to understand the pain of people with PD with appropriate methods.

Key words: Parkinson disease, Pain, Pain Measurement, Non-Motor Symptoms, Qualitative analysis;

INTRODUCTION

Parkinson's disease (PD) is characterized as a chronic, degenerative and progressive disease. First described in 1817 by James Parkinson as agitating paralysis, it is considered the most common form of movement disorder and the second most frequent neurodegenerative disease in the world, right after Alzheimer (1–4). In this disease, there is a progressive degeneration of nigrostriatal dopaminergic neurons, causing tonic, postural and mobility changes (5).

Worldwide, studies indicate that about 2% of the world population over the age of 60 has PD. In Brazil, the incidence is about 3.3% of the population over 64 years, 8.5% for people between 80 and 85 years and 14.3% for individuals over 85 years (6–10). Its etiology is not yet well understood, but it is believed that about 20% of cases are determined by genetic and/or hereditary factors and 80% by idiopathic or sporadic factors.(11,12)

Non-motor symptoms (NMS) sat so much since the onset of the disease in approximately 21% of people with PD (13). Among these symptoms, pain is one of the most frequent and debilitating, it is reported in about 50 to 85% of cases in this population (11,14–17). This symptom is more prevalent in women and is also related to the worsening of the disease, that is, the more advanced the staging of the disease, the more people with PD will report pain (18).

In this disease, pain can be classified chronologically as acute or chronic, where the first is described as a symptom that lasts up to three weeks and the second as a pain that persists or repeats for three months or more (19,20). In addition, pain may be of primary origin that is defined as pain in one or more anatomical regions that persists or reuses for more than 3 months, is associated with significant emotional distress and symptoms are not best explained by another diagnosis, or of secondary origin which is when this symptom derives from another diagnosis (20).

In general, there are three different mechanisms of pain: nociceptive, neuropathic and nociplastic pain. All of them are possible to occur in PD patients, in an isolated or mixed way. Nociceptive mechanism arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors; neuropathic is caused by an injury or disease of the somatosensory nervous system, and finally nociplastic arises from altered nociception, although there is no clear evidence of actual or threatened tissue damage, causing the activation of peripheral nociceptors or evidence of disease or injury of the somatosensory system that causes pain (21–23)

Chronic pain has been noted in PD since its original description in 1817 by James Parkinson in the upper limbs (MMSS) and it is believed that there is the intensification of these NMSs in the off period of dopaminergic treatment, enabling a correlation of the dopaminergic system with the central nociception of this population (24). Pain can predominantly modulate motor control, influencing the cognitive, perceptual, and motor areas of the upper order of the brain, and when it is present in people with movement disorders motor control may be deficient. (25)

Although there are already some studies that have assessed pain in people with PD, it is not yet clear what the characteristics of this pain are, even after more than 200 years since the first descriptions of the disease, especially about intensity, location, relief and worsening factors, a chronology of the manifestation of this symptom and the type of mechanism. Therefore, the present study aims to characterize pain in people with PD and verify instruments that have been used to measure and classify pain.

METHOD

The protocol defined for this systematic review adhered to the recommendations proposed *by The Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA) (26). This study was submitted to (26)*the International Prospective Register of Systematic Reviews* (PROSPERO), registration number CRD42021243043. The question of this review is "What are the pain-related characteristics in people with Parkinson's disease?". This study was structured with the PECO strategy: P. Population of interest - Parkinson's disease; E. Exposure - Pain; C. Control - People without PD; O. Outcome - Characteristics of pain (27).

Inclusion and exclusion criteria

Cross-sectional, longitudinal, case-control, cohort and population-study observational studies were included, with no language or date of publication restriction. However, studies that targeted people with parkinsonism or Parkinson's disorders and who presented neurological alterations related to COVID-19 and/or SARS-CoV-2 were excluded.

Search strategy

The research was conducted in nine databases to find studies that meet the criteria of this study: *National Library of Medicine (MEDLINE-PubMed), Scielo,*

Lilacs, Cochrane, PEDro, PsycINFO, SPORTDiscus, Web of Science (WOS) and *Scopus*. In addition to these, we conducted the research in the *Google Scholar*, where the first 100 articles of the search performed were selected, and the *Hand Search*, which is the search in the references of the included studies for potential articles to be selected. The search strategy used was the combination of the terms used as descriptors "*Parkinson disease*" and "*Pain*" with the boolean operator "*AND*" in each database as described in table 1. Search was ended at until April 18, 2022.

For the PEDRO databases, two forms of the search were performed after a difference in the number and titles of the articles found in the databases was observed ("PEDro: Search," [s.d.];). See details in table 1. Some of the selected studies do not clearly describe the type of study, so the investigators of the present study (EOM? and MIOD) made this decision according to the methodological design.

Data extraction

All articles found were evaluated sequentially for titles, abstracts and complete texts, by two reviewers (EOM and MIOD), separately and independently, according to the inclusion and exclusion criteria of the present study. The data of the selected articles were recorded in a standardized way by the evaluators in an Excel spreadsheet®. For articles in which there was a conflict of opinion between the evaluators, it was decided in consensus with the participation of a third senior evaluator (JMS). For studies in which the data were inconclusive or incomplete, the authors were asked to send the data in full with a response period of 15 days or the article would be excluded.

Authors' names, study title, hypothesis, objectives, sample calculation, description and anumber of participants, variables investigated, instruments used and the following outcomes were collected: pain mechanism (neuropathic, nociceptive, nociplastic, mixed and unidentified); site of pain; time of pain; pain intensity; relief and exacerbation factors; pain chronology (acute or chronic pain); origin of pain (primary or secondary); pain terminology reported in inclusion criteria; pain terminology presented in the results.

Assessment of the risk of bias

The tool published by *the National Heart, Lung and Blood Institute* (NHLBI) (30). The assessment of the risk of bias was performed independently by the

two evaluators. For cohort or cross-sectional studies, this tool consists of 14 items - each of which can be marked as Yes (Y), No (N), and Unreported (NR) or Unapplicable (NA) or Cannot Determine (CD). For case-control studies, it consists of 12 items - each of which can be marked in the same way previously mentioned. To represent the results obtained from the aassessment of the risk of bias of the studies, the investigators used the table form and colorimetry to describe the markings of each item and thus it is possible to have a better visualization, so the green color was applied to Yes (Y), the red color to No (N) and, finally, yellow to Not reported (NR) or Not applicable (NA) or Cannot Determine (CD).

Data analysis

After data extraction and bias risk analysis, quantitative analysis was performed, through the metadata generation of the included studies that presented instruments for measuring similar outcomes (pain). The instruments analyzed were BPI (severity and intensity), VAS and KPPS. The heterogeneity of the studies was verified by the test of the same name (I2) and a value of $p \leq 0.05$ was considered statistically significant. Moreover, the random effect was applied due to the high heterogeneity presented by the characteristics of the studies. Except when overlap occurs, as observed in the sub-group analyses related to Brief Pain Inventory data.

The meta-analyses were performed using Cochrane Collaboration's Review Manager version 5.3.5 software, the official device of the Cochrane Informatics & Knowledge Management Department.

RESULTS

According to the search strategy described, 1 4,197 articles were found, excluded 11,652 based on inclusion criteria and 2,269 were duplicated. Finally, 94 articles published until April 18, 2022, were selected, with 66 cohort and cross-sectional studies, and 28 case-control studies. Details about the selection of the articles are described in Figure 1. Supplement 1 featured all articles included.

A total of 30,219 people participated in the included studies, 24,593 people with PD and 5,626 controls. Controls were multiple and can be represented by spouses and caregivers (31), people with osteoarthritis (32), post-stroke (33), neuromuscular diseases (34), and cancer, chronic pain or diabetes patients, but without a diagnosis of basic neurological disease (35), and healthy volunteers matched by age and gender

(32,36–61). The sample size ranged from 11 to 4,086 participants with PD and from 11 to 1,960 controls.

Supplement 1 describes all the instruments used in each study to evaluate the participants. Thirty different validated instruments were used to assess the pain of the participants, i.e.: Pain assessment analysis; Leeds Evaluation of Neuropathic Symptoms and Signs (LANSS); Ford classification; Pain diary; Non-Motor Symptom Scale (NMSS); King's Pain Scale in Parkinson's Disease (KPPS); Likert scale of points; Numerical Pain Scale (NPS); Numerical Classification Scale (NCS); Visual Analog Scale (VAS); *Facial Action Coding System* (FACS); Pain Disability Index (PDI); Oswestry disability index (ODI); Michigan Neuropathy Screening Instrument; Brief Pain Inventory (BPI); Central Awareness Inventory; Electric pain threshold; Heat pain threshold; *Pain detect*; German pain questionnaire; 9-symptom Wear Questionnaire (WOQ-9); McGill Pain Questionnaire (MPQ); Non-Motor Symptoms Questionnaire for PD patients (NMSQuest); King's Pain Questionnaire in Parkinson's Disease; Pain O-meter Questionnaire; Temporal summation of heat pain; and finally, the cutout of the pain domain of the Quality of Life questionnaires EQ-5D, Parkinson Disease Questionnaire–39 (PDQ-39), Short-Form (SF-12v2) and Short Form-36 (SF-36), and question 1.9 of the Unified Parkinson's Disease Assessment Scale of the Society of Movement Disorders Part I (MDS-UPDRS-I).

In addition to these validated instruments, participants were also evaluated through interviews regarding location, relief and worsening factors, the onset of pain symptoms, whether this symptom was before or after the diagnosis of PD, time of greater and lesser intensity, and interference in activities of daily living (ADLs).

Among the 24,593 people with PD who participated in the selected studies, 18,988 (77.20%) reported pain among NMS. Only 14 studies (31,34,48,49,62–71) defined the chronology of pain as acute or chronic pain, only one described the origin of pain as primary or secondary (72), and five articles presented the type of pain mechanism according to IASP (47,55,73–75). In addition, there was a great divergence in the terminology used to define pain characteristics in the inclusion criteria and in the results found. Details are in supplement 1. In the studies, authors defined the type of mechanism of this symptom according to the participants' reports, a large part of which used the Ford classification scale or KPPS (76,77), so a higher predominance of musculoskeletal pain was observed in people with PD (53,56,57,65,66,68,69,71,72,74,78–94). Kobylecki et al., (2020) observed that, in a

sample of 1909 participants, 76.6% had nociceptive pain and 8.3% neuropathic pain. Broetz et al. (2007) e Silverdale et al. (2018) identified that 38% (total n: 101) and 34% (total n: 1957) of the participants, respectively, also had neuropathic pain. Kinugawa et al. (2022)also observed neuropathic pain in the participants, but presented the data in intensity, showing that, in the off period, the intensity of neuropathic pain is higher than in the on period. Adewusi et al. (2018) also investigated the presence of neuropathic pain and observed a prevalence of 35.3% (total n: 51) among participants with PD. In addition, they identified the presence of allodynia, hyperalgesia and burning pain in 3, 7 and 11 participants, respectively.

Pain intensity reported by the participants, measured by the 11-point numerical scale or the visual analog scale, ranged from moderate to intense, i.e., > 4.07 out of 10 (7,31,33,34,45,48,50,55,56,59,68,85,92,96–104). However, there were also studies that observed the intensity of mild pain between 2.4 and 3.89 of 11 points (64–66,73–75,78,81,105–107). Quittenbaum & Grahn, (2004) identified the maximum pain intensity as moderate (5.1 out of 10 points) and the minimum as mild (2.2 out of 11 points). Lopes et al., (2021) identified that the mean pain intensity was considered mild in patients treated with antiparkinsonian medication (2.17±0.39) than in non-medicated patients (4.2±0.59). Gundogdu et al, (2016) described that people with PD have the intensity of musculoskeletal type pain greater than controls matched by age and gender, which does not bring quantitatively, but informs that this difference was not significant, so there was reporting bias.

De Mattos et al, (2019) identified pain intensity from mild to moderate, but also did not describe the data quantitatively. Skogar et al, (2012) bring the results of pain intensity in median (5.0 out of 10 points), so it was not possible to determine the level of pain intensity of the included participants, since the data from this instrument should be presented on average. Suzuki et al, (2018) identified that 55.9% (total n of 159) of people with PD and headache, and 42.8% (total n of 42) of people with PD and migraine also have moderate to severe pain intensity. Some studies have described the use of the instruments mentioned above but did not describe the quantitative and/or qualitative data in the results (79,82,83,111,112).

Back and/or lumbar region was the most cited pain site among the participants of the included studies (31,33,34,53,59,63,64,69,71,72,83,85,98,102,103,107,108,112–114). Other regions were also cited, such as head and neck (70,110,115–119), lower

(50,82,88,92,99,100,120) and upper limbs (58,68,84,91). Martinez-Martin et al. (2019) observed that 50.2% (total n: 300) of their participants felt pain in the upper and lower limbs during sleep. Skogar et al. (2012) identified that more than 30% (total n of 28) of women with PD feel pain in upper limbs and 21% to 30% (total n of 16) of men feel pain in the lower limbs. It is noteworthy that some of the studies cited already had the objective of studying to investigate a single specific pain region.

Some studies have identified that 5.5% to 53% of its participants showed that pain arose before the diagnosis of PD (58,62,64,89,99,121,122). Worsening pain has also been observed with the progression of the disease (48,71,83,90). However, Lin et al. (2016) e Polli et al. (2016) observed that the younger the person and/or shorter the disease, the greater the intensity of pain. Nguy et al. (2020) described that increased disease duration is associated with worsening musculoskeletal pain and nocturnal pain.

Patients during the *off-time* or at the moments of fluctuation presented greater intensity of pain (56,57,68,85,111,121,123–125). Therefore, it was observed that pharmacological treatment with antiparkinsonian therapy, non-steroidal anti-inflammatory drugs, analgesics, opioids and neuroleptics can relieve pain in people with PD (62,80,86,89,90,101).

Other studies (32,36–42,44–46) have identified dystonic pain, defined as pain associated with sustained twisting movements and postures, muscle contractions that are often very strong and painful, and may involve any limb or extremity, as well as facial and pharyngeal musculature, and may also fluctuate closely with medication dosage, as the most prevalent; people with PD were more frequently to describe the pain as exhausting, tiring, penetrating and miserable; increased propensity to experience pain in membros inferiores e superiores; people of Caucasian origin with PD are more likely to experience pain than people of Indian origin with PD; people with PD and osteoarthritis tend to report pain as more intense and irradiated; when single, people with PD have greater intensity and interference of pain in their activities than married ones.

Regarding the methodological quality of those 28 studies included in the case-control type, methodological failures were detected in all cases, being characterized between moderate and low quality. The main flaws detected were the absence of sample size calculation; lack of random selection of study participants; non-use of concurrent controls; exposure assessment before measuring the result; and concealment of the evaluators. For this type of study, the methodological quality

assessment tool used evaluates the possibility of 12 methodological failures, however, only 11 studies of the 28 included had a few fewer than six failures detected (36–42,46,51,74,126), the lowest number of failures detected in the same study were four (42). Details can be seen in Figure 2.

Regarding the methodological quality of the 66 studies including cohort and cross-sectional, methodological flaws were found in all studies and can also be considered as moderate to low quality. The most frequent failures detected were the percentage of inclusion of eligible participants greater than 50%, no sample size calculation, exposure assessment before result measurement, sufficient time to see an effect, repetition of exposure assessment, concealment of outcome evaluators and loss of follow-up below 20%. For cohort and cross-sectional studies, this tool evaluates the possibility of 14 methodological failures and only eight of the 66 studies included had fewer than seven failures detected (31,70,98,109,127–130). Only three studies had the lowest number of failures detected in the same study, which were five (70,127,128). For details, see Figure 3.

Only five of the 94 articles evaluated the pain of people with PD in a similar way through the BPI (36,38–41), but one of these five did not evaluate pain interference (40). The studies showed that the control group tends to feel more pain than the DP group both in severity ($Tau^2 = 9.08$; $Chi^2 = 23.95$, $df = 4$ ($P < 0.0001$); $I^2 = 83\%$; Test for overall effect: $Z = 3.98$ $P < 0.0001$) as for intensity ($Tau^2 = 10.30$; $Chi^2 = 8.78$, $df = 3$ ($P = 0.03$); $I^2 = 66\%$; Test for overall effect: $Z = 5.01$ $P < 0.00001$). Details in Figures 4 and 5.

Two other publications reported similar pain assessment in people with PD through KPPS (47,55). However, there was no evidence that this instrument describes pain of this population ($Tau^2 = 3.35$; $Chi^2 = 23.55$, $df = 1$ ($P < 0.00001$); $I^2 = 96\%$; Test for overall effect: $Z = 1.50$ $P = 0.13$), figure 6.

Similarly, two other studies evaluated pain intensity of people with PD with VAS (31,50), however, it was also observed that there is no evidence that this instrument has specificity to evaluate this characteristic of this population ($Tau^2 = 0.09$; $Chi^2 = 11.76$, $df = 1$ ($P = 0.0006$); $I^2 = 91\%$; Test for overall effect: $Z = 0.77$ $P = 0.44$). Details in Figure 7

Trying to avoid overlap interference, taking into account that only the studies of the same author allowed the execution of the (36,38–41) meta-analysis, the fixed effect was used for the analysis of the BPI subgroup, presenting the following

results for pain severity ($Tau^2 = 9.08$; $Chi^2 = 23.95$, df = 4 ($P < 0.0001$); $I^2 = 83\%$; Test for overall effect: $Z = 3.98$ ($P < 0.0001$)), pain intensity ($Tau^2 = 10.30$; $Chi^2 = 8.78$, df = 3 ($P = 0.03$); $I^2 = 66\%$; Test for overall effect: $Z = 5.01$ ($P < 0.00001$)) and total ($Tau^2 = 12.06$; $Chi^2 = 44.56$, df = 8 ($P < 0.00001$); $I^2 = 82\%$; Test for overall effect: $Z = 5.73$ ($P < 0.00001$); Test for subgroup differences: $Chi^2 = 2.68$, df = 1 ($P = 0.10$), $I^2 = 62.7\%$). Thus, we can observe that there is evidence that the evaluation of pain intensity with BPI can portray the pain of people with PD, since a heterogeneity of 66% was found for this subgroup, although in both subgroups the control group presented greater pain in relation to the PD group as can be observed in Figure 8.

DISCUSSÃO

Among the almost 15,000 articles found, 94 were selected, 28 of the case-control type and 66 of the cohort and cross-sectional type, of which included an analysis of 24,593 people with PD and 5,626 controls. A large variety of instruments (n=30) were used to assess pain in people with PD. The most used were VAS, NDT, BPI, KPPS and MPQ. The main characteristics of pain found in people with PD were mostly musculoskeletal pain, with moderate to severe intensity, mostly in the back region, which is possibly the initial symptom of PD and that tends to intensify with the worsening of the disease and there is relief with antiparkinsonian pharmacological therapy.

Regarding the type of pain mechanism in people with PD, several of the selected studies used definitions such as musculoskeletal, radicular, dystonic, central or primary, akathisia, chronic, related to fluctuation, nocturnal, orofacial or discoloration and edema, according to the Ford Classification and KPPS (76,77). IASP, on the other hand, describes that the type of pain mechanism can be defined as neuropathic, nociceptive and nociplastic (23). Also, mixed pain is defined by the combination of two or three types of pain (131). Among the 94 selected studies, only five followed the IASP terminology (33,47,95,107,111). Thus, it is suggestive that the evaluation used was not adequate, since they follow inadequate classifications and do not follow the concepts of IASP, impacting on the unfeasible of these studies as evidence for the elaboration of a treatment plan.

Theoretically, pain in people with PD could be characterized as the type of mixed pain, since they have the report of pain in a non-neural tissue, but there may also be an injury to the somatosensory system and also have altered nociception, that is,

nociceptive, neuropathic and nociplastic pain, respectively. Other motor disorders may also have the characteristic of mixed pain such as chronic low back pain, fibromyalgia and chronic osteoarthritis (132,133). Therefore, following the current concepts of IASP, pain in people with PD may be mixed and there is a need for further studies to evaluate with appropriate instruments the type of pain mechanism of this population so that we have evidence of this characteristic.

Pain can be evaluated at various times during the anamnesis of the person, so it can be quantified at rest, movement, right after an activity, because several factors can influence it (134). Among the 94 studies included, none describe the exact moment when the pain of people with PD was evaluated. Given the methodological designs of the selected studies, it assumes that it was at rest due to only a single evaluation being performed and not describing details that may have happened during the movement. However, it is necessary to better control all factors that can influence pain in people with PD so that it is possible to characterize it adequately.

Currently, several instruments have been described as appropriate to evaluate pain intensity such as VAS, END, BPI, MPQ, among others (135–138). There is a need to use the appropriate instrument for pain assessment so that the result obtained is reliable and consistent with what was proposed. There were studies that intended to determine the pain intensity outcome, but used instruments that are not adequate or used cutouts of instruments suitable for other variables or even not validated, so it was not possible to interpret the data of these studies for the characteristic cited.

The highest reporting rate regarding the region with the highest intensity of pain was the lumbar. This may be related to one of the main SMs which is postural instability, since the anteriorization of the gravity center occurs as a form of compensation, in addition it may be associated with other MS which as a result will decrease motor control (139). In low back pain, there may be different pathophysiological mechanisms leading to inflammatory-nociceptive, neuropathic or central dysfunctional conditions, being considered as mixed pain involving both nociceptive and neuropathic mechanisms (133).

The MS of this population tends to cause postural, balance and gait changes, which impacts on the decrease in motor control (140). In addition, peripheral neurodegeneration of the basal ganglia also causes this motor deficit (141). When the individual has experienced pain or has the knowledge that he will feel it, he moves

differently by donating postures and movement patterns that minimize this symptom, even momentarily (25). Thus, people with PD have a severe decrease in motor control both due to the worsening of the disease, as well as by the persistence and worsening of pain, in addition to other different conditions that are also prone to this.

IASP defines pain as an unpleasant sensory and emotional experience associated with or similar to a real or potential tissue injury and may be related to biological factors (23). Some studies have observed that people with PD may experience pain with one of the first symptoms of the disease (58,64,99,121,122,142). This may be related due to the initial damage of atrophy of the neurons of the black substance and decreased dopamine production, along with the initial manifestations of SMs (143).

When the reports of intensity, location, terms to describe pain and worsening with the progress of the disease are observed, it is suggestive of the increase of central and peripheral nociceptive responsiveness, therefore, central and peripheral sensitization impacting the decrease of the pain threshold in this population. Only one study among those included evaluated the central sensitization of people with PD which corroborates that the pain of this population is related to this symptom (79). However, more studies need to better investigate the association between these variables in people with PD.

Among the various instruments used to evaluate pain characteristics in people with PD, it was only possible to qualitatively analyze only three: BPI, KPPS and VAS. However, for KPPS and VAS, there was no evidence that they can portray the pain of this population and there was also a very high heterogeneity among the studies, which reinforces this analysis, besides that it was only possible to perform the meta-analysis with only two studies for each of the instruments, and 15 publications of the 94 included used KPPS and 29 VAS.

With the BPI analysis, we observed that there is evidence that it is an instrument that is sensitive to assess pain characteristics in people with PD, however, the control group presented higher intensity and severity of pain than the target population. The studies eligible for the meta-analysis with this instrument were from the same group of authors and from the same sample, varying only in the number of participants in each publication, assuming a probable *overlap of* the participants. Thus, we cannot say that the BPI is actually an instrument that portrays the pain of people

with PD or whether the data found was inaccurate because it is the same sample analyzed repeatedly.

When the bpi pain severity subgroup was analyzed, high heterogeneity was found and the controls present more severe pain than people with PD. However, when this characteristic is evaluated, it should be observed that it is directly related to the cognitive state of the patient and one of the NMS of PD is cognitive impairment and this happens in a similar way with VAS. However, we found that both the bpi pain severity subgroup and VAS have no evidence to assess the pain of people with PD.

With the pain intensity subgroup of the BPI, it was the only one that there was positive evidence that portrays this pain characteristic of people with PD, mainly because it presented low heterogeneity even with the overlap, but the controls used presented higher intensity than people with PD. This subgroup is similar to the NPS, which is a simpler instrument to be used to assess the intensity of pain in this population, but it was not possible to perform the meta-analysis with the studies that used this instrument. Thus, it is possible to reinforce the hypothesis that more complex or requiring more cognitive function has lower sensitivity and accuracy to determine the characteristics of pain in people with PD.

The included studies had several limitations. Several studies did not use an appropriate control group when evaluating people with chronic neurological diseases or that affect movement, or even when using participants who have ties to the target population. The methodological quality of the studies was low in most cases, only 18 of the 94 had less than 50% of methodological failure. Only three studies calculated the sample size for the recruitment of participants, and also only three other studies blinded the evaluators. Several selected studies did not use adequate instruments for pain assessment. Some studies have described the use of some evaluation instruments; however, they do not present their results. Another limitation present in this study was the difficulty in obtaining the articles in full.

As strengths we can highlight that this review is the only one that describes the main characteristics of pain in people with PD; this study brings several gaps to be evaluated as the type of pain mechanism in people with PD, pain as an initial symptom of the disease and the justifications for the regions with higher intensity of this symptom. This review also describes that the methodological quality of studies that evaluated pain in people with PD was moderate to low, showing that the next studies require greater methodological rigor for their execution. This study describes the main

assessment instruments that were used to assess pain in people with PD and, mainly, there is no standardization to characterize the pain of these people.

Future studies should seek to better understand NMS pain in people with PD, build an appropriate evaluation method for this symptom by following the IASP terminologies for the definition of the type of pain mechanism, use appropriate instruments that characterize pain, investigate the factors of relief and worsening of this symptom, so that it is possible to better understand about pain in people with PD.

CONCLUSIONS

In the present study, we observed that most people with PD feel pain with moderate to severe intensity, with a type of mixed mechanism, especially in the lumbar region and that relieves with the pharmacological treatment antiparkinsonian, that pain can be one of the first symptoms and has worsened with the progress of the disease. However, it was observed that there is no pattern to characterize pain in people with PD since it is a symptom present in most of this population, but there are not sufficiently specific and sensitive instruments to determine and quantify these characteristics compared to different controls. For these reasons, it is necessary that further studies be carried out in order to be able to perform the characterization of pain in people with PD.

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FIGURES

Figure 1: Flowchart of the selection of articles.

Figure 2: Evaluation of the methodological quality of case-control articles, following the 12 items of the quality evaluation of case-control studies published by the NHLBI. Y (yes), N (no) or NR (not reported), NA (not applicable).

Figure 3: Evaluation of the methodological quality of cohort and cross-sectional observational articles following the 14 items of the Quality Assessment of cohort and cross-sectional studies published by the NHLBI. Y (yes), N (no), or NR (not reported), NA (not applicable).

Figure 4: BPI forest plot - pain severity. The severity of pain compared to the control group with the DP group using BPI.

Figure 5: BPI forest plot - pain intensity. Pain intensity compared to the control group with the DP group using BPI.

Figure 6: Forest plot of KPPS. Evidence of the use of KPPS to assess the pain of people with PD compared to the control group

Figure 7: Forest plot of the VAS. Evidence of the use of VAS to assess the pain intensity of people with PD compared to the control group

Figure 8: Forest plot of BPI subgroup analysis. Evidence of pain severity, pain intensity and total, respectively.

TABLES

Table 1 - Combinations of the descriptors and filters selected in each database used. WOS: Web of Science

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	ok
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	ok
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	ok
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	ok
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	ok
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	ok
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	ok
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	ok
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	ok
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	ok
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	ok
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	ok
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	ok
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	ok
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	ok
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	ok
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	ok
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	ok
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	ok

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	ok
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	ok
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	ok
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	ok
Study characteristics	17	Cite each included study and present its characteristics.	ok
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	ok
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	ok
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	ok
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	ok
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	ok
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	ok
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	ok
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	ok
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	ok
	23b	Discuss any limitations of the evidence included in the review.	ok
	23c	Discuss any limitations of the review processes used.	ok
	23d	Discuss implications of the results for practice, policy, and future research.	ok
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	ok
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	ok
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	ok
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	ok

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	ok
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	ok

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

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Table 1

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Table 1 - Combinations of the descriptors and filters selected in each database used.

Base	Descriptors
COCHRANE	**Parkinson disease AND pain**
GOOGLE SCHOLAR	Parkinson disease AND pain
LILACS	**Parkinson disease [words] AND pain [words]**
PEDRO (search advanced)	Parkinson disease AND pain
PEDRO (search simple)	**Parkinson disease AND pain**
PSYCINFO	Parkinson disease AND pain
PUBMED	**("Parkinson disease" [Mesh]) AND "Pain" [Mesh]**
SCIELO	(Parkinson disease) AND (pain)
SCOPUS	**Parkinson disease AND pain (review, article)**
SPORTDISCUS	Parkinson disease AND pain
WOS	**Parkinson disease AND pain (review, article, data paper)**

Figure 1

Click here to access/download;Figure;Figure 1.tif

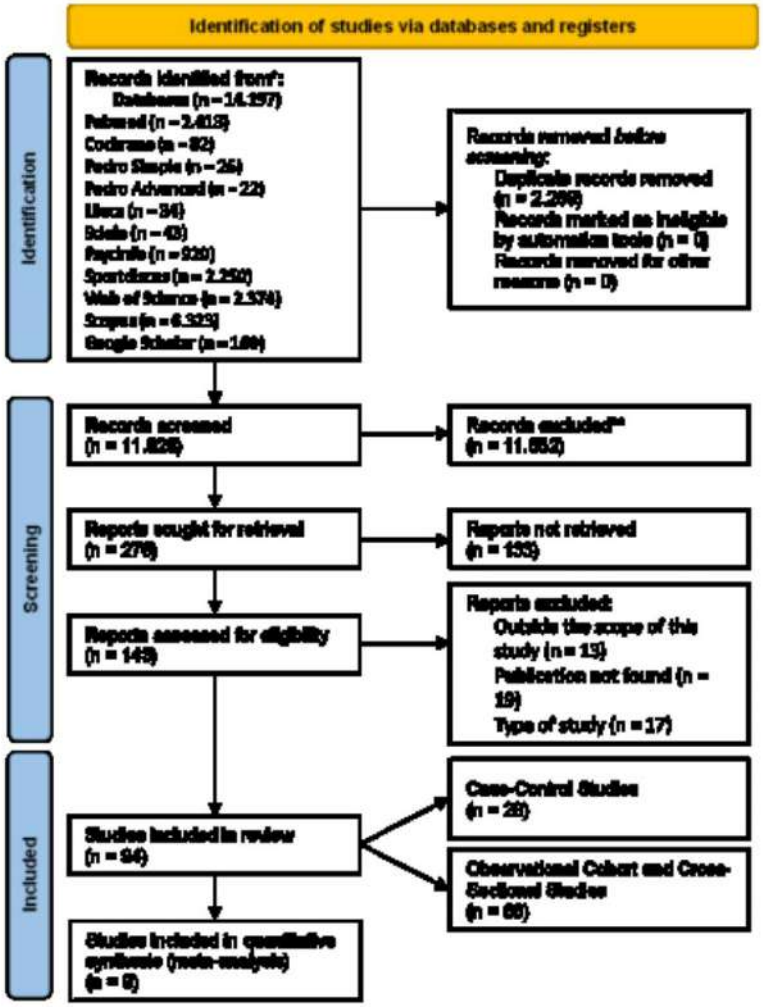

Figure 2

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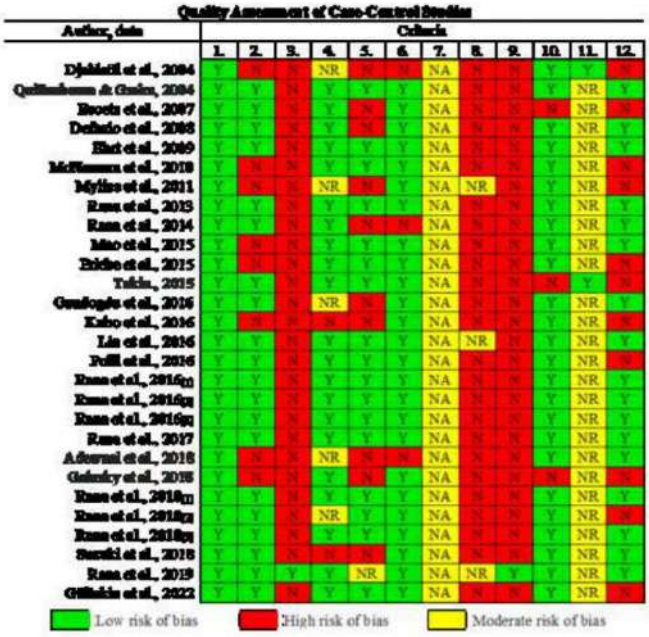

Figure 3

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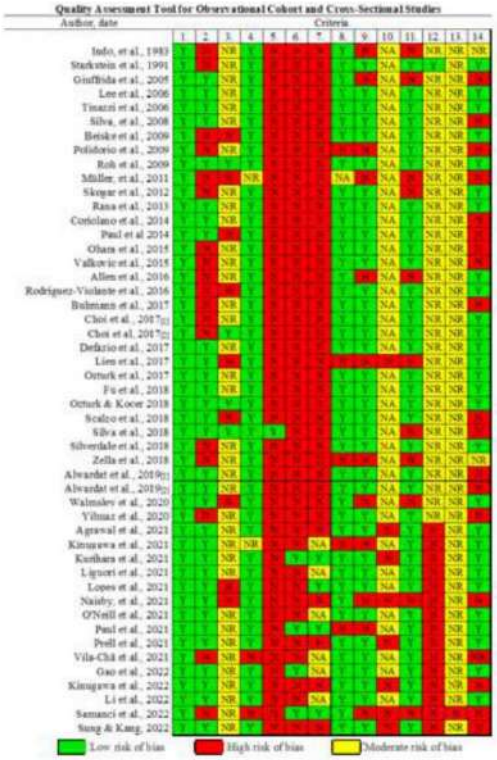

Figure 4

Click here to access/download;Figure;Figure 4_Forest plot.png

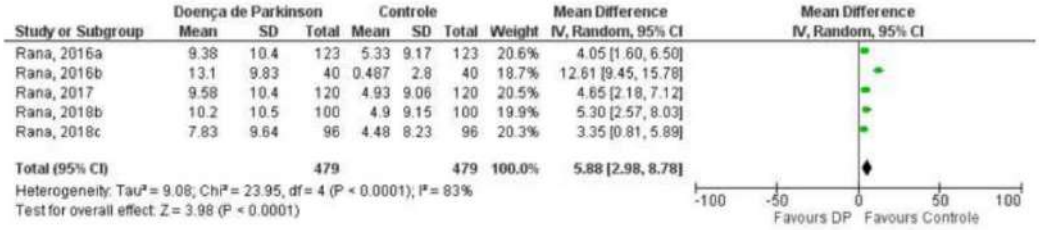

Figure 5

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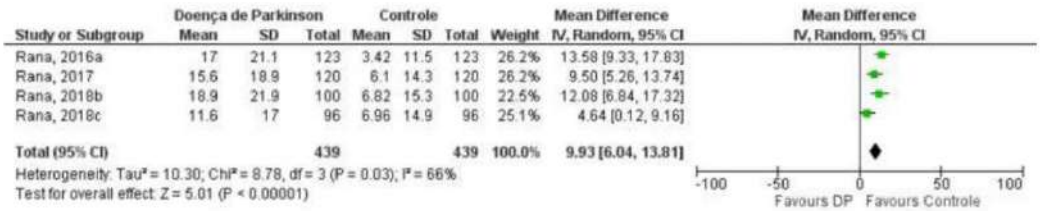

Figure 6

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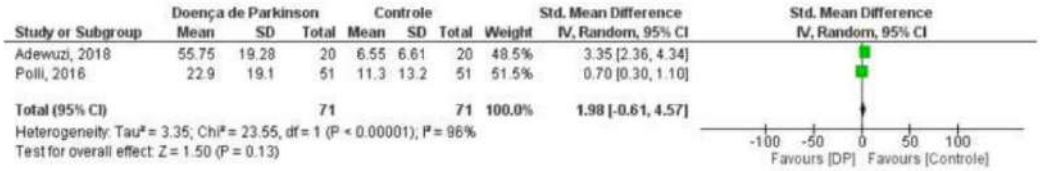

Figure 7

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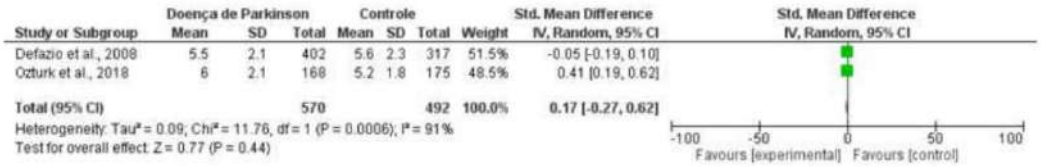

Figure 8

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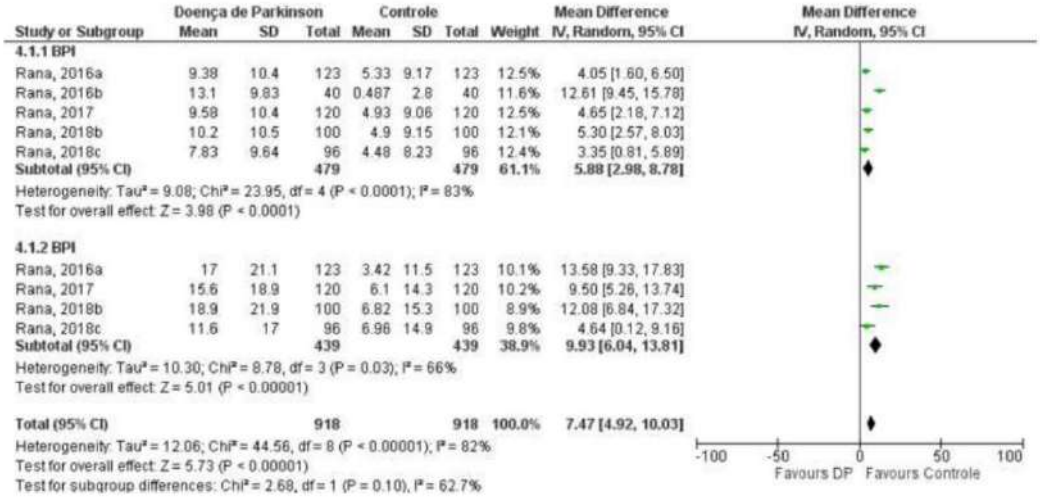

Supplement 1

Table 2 - Details of the main information of the articles included

Author, date	Type of Study	Participants	Variables	Assessment instruments	Main results
Indo et al., 1983	Cross-sectional observational	71 people with PD	Characteristics of headaches †	Questionnaire †	Headache was observed in 8 of 24 male and 17 of 47 female patients (35.2% overall). The total number of headache cases classified by part (one case may appear in more than one part) was: nuchal region (n=10), temporal and occipital regions (n=8 each), frontal region (n=5) and entire head (n=1). As for the nature of the headache, dull pain was the most frequent (16 out of 25 cases of headache), followed by eight cases of throbbing pain. Diurnal headache variations were observed in 12 cases (48%) but were mild in all but one case.
Starkstein et al., 1991	Cross-sectional observational*	79 people with PD	Depression Diagnosis of mental disorders Neurological examination cognitive function Pain † Sleep	Hamilton Depression Scale DSM-III PSE NWDE MMSS Pain questionnaire McGill 's Questionnaire SQ	A stepwise regression analysis was performed, with the McGill Questionnaire or the SQ as dependent variables, and age, disease duration, levodopa dosage, tremor, rigidity, amnesia, MMSE, NWDS, and PSE as independent variables. Patients in the MA group had significantly higher SQ scores (ie, more sleep disturbances) than the NO group. MPQ scores were also significantly higher (ie, more

1

					severe pain) in patients with MA compared to patients with MI and NO. MPQ analysis showed a similar frequency of pain in the three groups.
Djaldetti et al., 2004	Observational case-control*	36 people with PD 28 healthy controls	Mechanical sensory threshold Pain intensity Pain sensitivity Thermal sensitivity	Von Frey filaments VAS Heat pain thresholds † Peltier based contact †	Mechanical thresholds and thermal sensitivity did not differ in both patient and control groups, nor between sides. Heat pain threshold was lower in PD patients who experienced pain compared to those who did not and those who experienced pain on the most affected side. In patients with fluctuations there were no lateral differences in thermal sensitivity and heat pain threshold or between "*on*" and "*off*" periods.
Quittenbaum & Grahn, 2004	Observational case-control* Controlled, Transversal Descriptive	57 people with PD 95 healthy controls	Pain intensity Pain part Quality of life	VAS Pain drawing SF-36	The pain problems are common in PD patients and largely in the healthy population. HRQoL was reduced for patients with PD in all SF-36 scales and consequently also in the pain dimension.
Giuffrida et al., 2005	Cross-sectional observational* Retrospective	388 people with PD	Pain† Topography of pain	Questionnaire † Self-report	Diagnosed with dopa-responsive Parkinson's disease, 269 (67%) had sensory or pain syndromes. Among them, 94% had muscle pain: stiffness (85%), pseudo cramps, spasms (3%) or various myalgias (7%); 51% had "rheumatological" osteoligamentous pain, articular (23%), periarticular

					(3%) or spinal (31%), but less defined and localized neurogenic pain syndromes were less frequent (8%), such as paresthesia (6%), dysesthesia (<1%), burning sensation (2%), itching (<1%), ill-defined discomfort (6%) or heaviness (1%), with segment (86%), axial (54%), radicular or pseudo radicular(14%), distal acral (4%) or less frequently anorectal or visceral distribution. Restless legs or akathisia were occasional (10%). Headaches and facial pain were less frequent (1%) and phantom pain was not found. More than a quarter were present at disease onset, and only (3%) of them resolved during disease development. About a third were clearly linked to motor fluctuations, most occurring in the off phase (34%). No correlation was found with age, sex, duration or stage of disease, L-dopa equivalent dose, depression, insomnia or autonomic dysfunction.
Lee et al., 2006	Cross-sectional observational	123 people with PD	Depression Pain †	BDI PACA BPI VAS Self-report	Patients reported 285 pains (median of 2 per patient) and 22.8% had 4 or more pains. The pain was reported as a problem in 85% and related to ILD in 62.6% of patients, unrelated to ILD in 64.2%, indirectly related to ILD in

			Cognitive Function Stage of disease	MMSE Hoehn-Yahr	8.1%, related to multiple causes in 4.1 % and related to treatment in 0.8%. Non-ILD-related pain was more common, more constant, and more severe than ILD-related pain. Overall, analgesic use was low.
Tinazzi et al., 2006	Cross-sectional observational	117 people with PD	Depression Duration and location of pain Pain intensity SMS	BDI self-report VAS UPDRS	The pain was described by 47 patients (40%) and can be classified as dystonic (n:19) and non-dystonic (n:16); in 12 patients both types coexisted. Logistic regression models of multiple explanatory variables indicated a significant association between pain and motor complications. No association was found between pain, dystonic or non-dystonic, and the other investigated variables, including medical conditions known to be associated with pain in the general population. There was a significant correlation between pain severity (measured on a Visual Analog Scale) and severity of motor complications (UPDRS part IV).
Broetz et al., 2007	Observational case-control*	101 people with PD 132 people post-stroke or	Radicular pain	Structured questionnaire †	The prevalence of back pain was 74% in PD patients (n 101) compared to 27% in control patients (n 132), but did not correlate with disease severity or duration. Mean back pain intensity

		with a brain tumor			(VAS 0-10) was 4.3 for PD patients and 1.3 for controls. Both radicular and non-radicular types of back pain were more frequent, and back pain caused more impairment in PD patients. However, it is noteworthy that PD patients in our study did not receive more pain medication than control patients.
Defazio et al., 2008	Observational case-control	402 people with PD 317 healthy controls	Depression Pain intensity PD staging SMs and SNMs Timeline and location of pain	BDI VAS Hoehn-Yahr UPDRS Self-report	The overall frequency of pain was significantly higher in PD patients than in controls (281 [69.9%] vs 199 [62.8%]), mainly because the healthy control group did not have dystonic pain. On the other hand, the frequency of non-dystonic pain was similar between PD patients and controls (267 [66.4%] vs 199 [62.8%]). However, we observed a significant association between PD and non-dystonic pain, starting after the onset of parkinsonian symptoms. Cramping and central neuropathic pain were more frequent among PD patients than controls. About a quarter of patients who experienced pain reported the onset of pain before starting antiparkinsonian therapy.

Silva, et al., 2008	Cross-sectional observational* prospective	50 people with PD	Dependence on a caregiver Disease severity Pain † SMs	Schwab and England's scale Hoehn-Yahr Questionnaire † END UPDRS	Twenty-eight patients reported pain; comparing the group with pain and the group without pain, there were no differences related to disease onset and PD motor symptoms. However, many patients reported improvement in pain when antiparkinsonian therapy was started or adjusted.
Beiske et al., 2009	Cross-sectional observational*	176 people with PD	Cognitive function Disease severity Pain† PD characteristics, demographics and somatic sensitivity	MMSE Hoehn-Yahr BPI [items 3,4,5 and 6] 10-point Likert scale Pain domain of the SF-36 Structured pain questionnaire Questionnaire†	The pain was reported by 146 (83%) patients. Compared with the general population, patients with Parkinson's disease experienced significantly more pain, as measured by the SF-36 Body Pain Scale. The average pain in the last 24h measured by the Brief Pain Inventory was 2.85. Fifty-three percent of patients reported one, 24% reported two, and 5% reported three types of pain. Musculoskeletal pain was reported by 70%, dystonic pain by 40%, radicular neuropathic pain by 20%, and central neuropathic pain by 10%. Thirty-four percent were on analgesic medication. The pain was not associated with age, duration of illness, or severity of illness; female gender was the only significant predictor of pain. Pain is frequent and disabling, regardless of demographic and clinical variables, except for

					females, and is significantly more common in Parkinson's patients compared to the general population. A minority of Parkinson's disease patients with pain received analgesic medication.
Ehrt et al., 2009	Observational case-control	227 people with PD 100 healthy controls	Cognitive function Depression Pain† SMs	MMSE BDI MADRS NHP UPDRS	Sixty-seven percent of PD patients suffered from pain, compared to 39% of the control group. PD subjects with pain had higher MADRS and BDI scores and were more likely to have major depression, than PD subjects without pain. In multivariate analyses, the presence of pain was significantly associated with depression scores, even after adjusting for demographic and clinical variables.
Polidorio et al., 2009	Cross-sectional observational	15 patients with PD 15 healthy controls	Impact of pain on PD	McGill 's Questionnaire	The pain was reported in 53% of GI (n=8) and 47% of GII (n=7). A small increase in negative responses about social and daily life was observed in GI. This impression did not reach a statistically significant difference in any of the McGill Questionnaire items.
Roh et al., 2009	Cross-sectional observational*	82 people with PD	Depression	Zung Depression Inventory	The PD with pain group had higher UPDRS part III scores, lower SF-36

			Pain intensity PD severity Quality of life SMs Somatic complaints/anxiety	VAS Hoehn-Yahr SF-36 UPDRS Modified Somatic Perception Questionnaire	scores, and higher Modified Somatic Perception Questionnaire scores than the pain-free PD group. The presence of pain, elevated Hoehn and Yahr stage, advanced age and somatic perception were the factors that negatively influenced the physical component of the SF-36. Depression and somatic perception were the most important predictive factors for the mental component of the SF-36. Depression and poor parkinsonian motor skills were the main factors contributing to pain.
McNamara et al., 2010	Observational case-control	23 people with PD 11 healthy controls	Humor Pain intensity SMSs and Medication Information Subjective pain complaints	DASS VAS Structured questionnaire McGill 's Questionnaire Pain Questionnaire	Both PD groups reported higher scores for current pain intensity, more evaluative pain intensity, and more overall pain than control participants. There was a significant association between mood and all McGill pain ratings in patients with left-sided onset PD, with those reporting more mood symptoms ranking higher on all pain scales. This association was not found in patients with the onset of PD on the right side.
Müller et al., 2011	Cross-sectional observational*	4086 people with PD	Pain intensity	EQ-5D (pain domain)	PD patients were divided into three groups according to their EQ-5D total score. There was an impairment of health status in relation to the increase

					in pain syndromes in patients with PD. There was a significant increase in VAS scores in relation to participation in the EQ-5D group. Female patients reported more pain and more frequently received drug treatment for pain than male patients. Significant associations were found between VAS and EQ-5D scores, and correlation coefficients were higher in men than in women.
Mylius et al., 2011	Observational case-control*	29 people with PD 27 healthy controls	Depression Cognitive function Disease severity Electrical pain threshold Nociceptive flexion reflex Thermal latency of pain Pain severity SMs	Geriatric Depression Scale 20 MMSE Hoenh-Yahr NFR Assessment of electrical pain thresholds Neurography sural Peltier based contact† Ford rating UPQRS	The data provided evidence that spinal nociception and pain sensitivity is preserved during the early phase of Parkinson's disease. After increased spinal nociception, experimental thermal and electrical sensitivity to pain increased during PD, while spinal nociception increased further. Increased sensitivity to experimental pain was observed in patients who had pain related to Parkinson's disease.
Skogar et al., 2012	Cross-sectional observational*	45 people with PD	Pain†	Pain diary Self-report VAS Pain Evaluation Analysis	In one-third of participants, pain preceded the PD diagnosis. The median pain score measured with a visual analog scale was 6.6 and 5.9 (for females and males, respectively) in the week prior to the study. In

			Quality of life Sleep disorders	Pain-O-Meter Questionnaire SF-36 PDSS	nearly half of the participants, the pain was present during all waking hours. Significantly more women described their pain as troublesome, while more men described their pain as irritating. Feelings of numbness and crawling at night were strongly associated with maximum VAS scores. Polypharmacy was common; 89% used anxiety/ insomnia medication and 18% used antidepressants. Only one-third of patients who reported pain relief with analgesics had them on their medication lists. Sleep was characterized by frequent awakenings. Urinary urgency and restless legs were frequently reported as nuisances. Patients rated their quality of life as significantly worse on all items compared to an age and sex-matched healthy reference population.
Rana et al., 2013 [1]	Cross-sectional observational	121 people with PD	Characteristics of physical pain Pain intensity	Questionnaires derived from the BPI VAS	The pain was reported by 80 (66%) patients with a mean age at PD diagnosis of 67.26±11.43 years. The most common clinical types of pain experienced by patients were dystonic pain (48%), paresthesia/neuropathic pain (36%) and musculoskeletal pain (28%). Patients with PD described their physical experience of pain as

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					pain (46%), feeling of tension (18%), sharp pain (12%), deep pain (12%) and dull pain (11%). Patients with PD affecting the right side of the body were four times more likely to report pain on the right side of the body; however, such a relationship was not found for the left side of the body. A higher score on the UPDRS-III scale and a longer duration of PD reduced the likelihood that patients would report bothersome pain. The presence of paresthesia/ neuropathic pain has been shown to decrease the likelihood that patients will report acute pain. No significant relationships were found between pain magnitude and sex, age at PD diagnosis, PD duration, UPDRS-III score, or Hoehn-Yahr stage of PD. Although 40% of PD patients felt that medication had a (direct) effect on their pain, no relationship was found between pain severity and PD medication.
Rana et al., 2013 [2]	Observational case-control	127 people with PD 127 healthy controls	Pain † Restless Legs Syndrome SMS	BPI Restless Legs Syndrome Severity Rating Scale UPDRS	The results showed that 21.3% of the PD patients had RLS, compared to only 4.7% in the control group, representing a highly significant difference. The pain reporting frequency was also significantly

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					higher among PD patients with RLS, but not in the control group. However, the mean difference in mean pain severity was not significantly different between PD with RLS and non-PD with RLS, nor were pain level and severity significantly correlated with severity in patients with right-sided onset of PD for both groups.
Coriolano et al., 2014	Cross-sectional observational	24 people with PD	Cognitive function Pain characteristics PD severity SMs	MMSE McGill 's Questionnaire Hoehn-Yahr UPDRS	The specific region of the body with the most frequent pain was the lumbar spine (50%). The regions categorized with the highest percentage of complaints were: the trunk (66.7%); upper (37.5%) and lower (37.5%) limbs. Most patients referred pain in only one body region, regardless of analyzing specific or categorized regions (37.5%). There was no significant difference in the proportional score achieved by each component of the McGill questionnaire score. Patients with PD in the akinetic rigid group had a greater number of painful body regions. Comparison between McGill index scores, according to the predominant symptom and according to the PD stage (Hoehn-Yahr) showed no significant difference.

Rana et al., 2014	Observational case-control	127 people with PD 127 healthy controls	Pain †	BPI Questionnaire †	Patients with PD were less likely to experience pain in both arms, more likely to show pain in both legs, and more difficulty localizing the pain. There was no relationship between duration of pain or arthritis and pain in PD. The likelihood of experiencing persistent pain, but not other forms, was much more strongly associated with PD patients than normal controls. When all other types of pain have been controlled, PD pain is most likely associated with akathesic pain.
Paul et al., 2014	Observational cohort	104 people with PD	PD severity Pain intensity SMS Type of pain	Hoehn-Yahr VAS UPDRS Ford rating	54.8% of patients with PD feel pain. Sensory symptoms were significantly associated with the group with pain (42.1%) than the group without pain (21%). The pain was more pronounced on the side with predominant motor symptoms (72%), and 68.4% of patients' pain responded to dopaminergic treatment. Musculoskeletal pain (82.5%) was the most common type and the lower limbs were the most common site of pain (43.2%).
Mao et al., 2015	Observational case-control*	142 people with PD healthy controls	Cognitive function Depression Disease severity Pain †	MoCA HAND Hoenh-Yahr VAS	The incidence of pain was 47.9% in PD patients, most with moderate levels of pain. Patients with pain had higher HRSD, UPDRS, Hoenh-Yahr and

			SMs SNs	Ford rating UPDRS NMSQT	NMSQT scores and lower MoCA scores compared to patients without pain. HRSD and NMSQT scores were closely related to pain.
Ohara et al., 2015	Cross-sectional observational*	186 people with PD	Depression Disease severity Electrical pain threshold Pain †	BDI Hoenh-Yahr PainVision® McGill's Questionnaire	A total of 186 patients completed the questionnaires. The average age was 74±9.3 years and the average for the Hoenh-Yahr stage was 2.8±0.8. Sixty-nine percent of the patients reported different types of pain symptoms. BDI scores were significantly higher in the pain group, despite the absence of statistically significant differences in mean age, Hoenh-Yahr stage and disease duration. Only patients with mild stage PD showed a significant difference in BDI scores between those with and without pain.
Priebe et al., 2015	Observational case-control	23 people with PD 23 healthy controls	Cognitive function Pain facial expressions Pain self-assessment Sensitivity to heat pain SMs SNMs	MMSE FACS Self-report Heat pain threshold Temporal summation of heat pain UPDRS NMSQT	We found a reduction in general facial activity in response to pain in PD patients on *Off*, which was less pronounced on *On*. Especially pain-relevant ocular narrowing occurred less frequently in PD patients than in controls in both phases, while frequencies of other pain-relevant movements, such as upper lip elevation (in *On*) and eyebrow contraction (in both phases), did not differ between groups. Furthermore,

					mouth opening (which is often not considered relevant to pain) was the most frequently exhibited movement in PD patients, while eye narrowing was the most frequent movement in controls. Not only general quantitative changes in the degree of expression of facial pain occurred in patients with PD, but also qualitative changes were found.
Tekin. 2015	Cross-sectional observational retrospective	128 people with PD 116 controls (participants' spouses or caregivers)	Pain in the injured limb	Structured questionnaire	Sixty-two subjects reported limb injuries before the onset of PD symptoms, 30 with and 32 without chronic pain (ie, ≥ 2 months). There was no association between injury and the side onset of PD in general. In subjects with chronic pain associated with limb injuries, however, the side of injuries was associated with the side onset of PD symptoms.
Valkovic et al., 2015	Cross-sectional observational*	100 people with PD	Depression Disease severity Neuropathic pain Pain † Quality of life	BDI Hoehn-Yahr LANSS BPI PDQ-8	A total of 76% of patients had pain. The following types of pain were present: musculoskeletal pain accounted for 41% of total pain, dystonic pain 17%, central neuropathic pain 22%, radicular pain 27% and other pain (non-radicular, arthritic, and visceral pain) accounted for 24%. One type of pain affected 29% of all subjects, two types 35%, three types

					10% and four types of pain were reported by 2%. All types of pain were more prevalent in individuals with advanced-stage PD than in individuals with early-stage PD, except for arthritic pain (subclassified under "other pain"). The frequency and intensity of actual, average, and worst experienced pain were significantly more severe in advanced-stage subjects. Individuals with PD with general pain and in advanced stages were more depressed and had worse QoL. Depression correlated with the worst pain in the last 24 hours and with the periodicity of the pain (the worst depression score in patients with constant pain). QoL correlated with mean pain in the last 7 days.
Allen et al., 2016	Cross-sectional observational*	231 people with PD	Disease severity Pain frequency Pain intensity Pain interfering with work	UPDRS Sum of items 37, 38 and 39 of the PDQ-39 6-point pain scale Item 21 of the SF-36 5-point pain scale SF-12v2 Item 5	The pain was reported by 187 (81%) participants, with 91 (39%) reporting pain of moderate severity or worse. Pain somehow interfered with work in 158 (68%) participants. After adjusting for age and sex, increased stiffness was associated with a higher frequency of pain and more pain that interfered with work. The tremor was not associated with any measure of

					pain, and motor impairments were not associated with pain severity.
Gundogdu et al., 2016	Observational case-control	112 people with PD 120 healthy controls	Pain intensity Pain part PD severity SMs	VAS Physical exam Hoehn-Yahr UPDRS	One hundred and twelve PD patients and 120 age- and sex-matched controls were interviewed by a rehabilitation specialist about their musculoskeletal problems. The prevalence of musculoskeletal pain was significantly higher in the PD group than in the control group. Body sites commonly involved were the lower back (46.4%), knee (21.4%) and shoulder (21.4%) in the PD group, and lower back (26.7%), knee (20. 0%) and ankle (11.7%) in the PD group. The lumbar region and shoulder were more frequently observed in the PD group than in the control group. In addition, the frequency of camptocormia, Pisa syndrome, hand and foot striated deformities ranged from 2.2 to 5.4% in patients with PD. Multivariate logistic regression analysis revealed that the presence of musculoskeletal pain was associated with female gender, older age and higher UPDRS II total score in the PD group, independent of Hoehn-Yahr stage, disease duration and medication.

Kubo et al., 2016	Observational case -control multicenter	324 people with PD 308 healthy controls	Pain intensity Pain part PD severity SMs	Item 7 of the SF-36v2 Body Illustration Hoehn-Yahr UPDRS	The prevalence of pain in the PD group was 78.6%, significantly higher than in controls (49.0%), as well as its severity. There was no correlation between the SF-36v2 score and motor scores such as UPDRS or Hoehn-Yahr scores. Pain distribution was similar between groups, predominantly in the lumbar region, followed by the gluteal region, legs, thighs, posterior region of the neck and shoulders.
Lin et al., 2016	Observational case-control	200 people with PD 200 healthy controls	Anxiety Cognitive Function Depression Neuropathic pain Pain intensity PD severity SMs State of physical pain	Hamilton Anxiety Scale MMSE Hamilton Depression Scale LANSS BPI Hoehn -Yahr UPDRS Pain domain of the SF-36	Of the 200 patients with PD, the pain was complained of by 106 patients (53%). According to the SF-36 Body Pain Scale, pain morbidity in PD patients was significantly higher than in the control group. The average pain in the last 24 h measured by the BPI was 2.67. About 76% of patients with PD had one type of pain, 21.7% had two types of pain and 1.9% had three types of pain. Furthermore, 69.8% of these patients had musculoskeletal pain, 4.7% had dystonic pain, 22.6% had radicular neuropathic pain, 20.8% had central neuropathic pain, and 9.4% had akathisia pain. Age at onset and depression were the most significant predictors of pain in PD patients. However, there was no significant

					association between pain and sex, age, disease duration or disease severity. Only 5.7% of PD patients with pain received treatment in this study.
Polli et al., 2016	Observational case-control	40 people with PD 15 healthy controls	Anxiety Cognitive function Depression Pain characteristics PD severity SMs	State trait anxiety inventory MMSE BDI-II KPPS VAS LANSS RMF Hoehn -Yahr UPDRS	The group with PD and persistent pain showed significant thinning in the bilateral temporal pole, left medial orbitofrontal cortex, bilateral left superior and inferior parietal areas, pars orbicularis and right superior frontal cortex, posterior cingulate and precentral cortex. There were no significant differences in subcortical volume and white matter between PD subgroups. Functional MRI showed a decrease in brain activity in the left inferior frontal orbital in PD patients with persistent pain, with greater activity bilaterally in the cerebellum and right inferior temporal areas. Only PD patients with persistent pain had hippocampus-accumbens disconnection without white matter and subcortical changes.
Rana et al., 2016 [31]	Observational case-control	123 people with PD 123 healthy controls	Anxiety Depression Pain intensity Pain interference Inability	HADS BPI Pain Disability Index	PD patients had significantly higher anxiety severity, depression severity, pain severity, pain interference, pain disability, and restless legs syndrome prevalence compared to controls. Furthermore, patients with PD and

			Prevalence of restless legs syndrome	Diagnostic criteria for restless legs syndrome	symptoms of anxiety and depression had significantly greater pain severity, pain interference, and pain disability, but no prevalence of RLS, compared to only patients with PD, anxiety with PD, and depression. with DP.
Rana et al., 2016 [2]	Observational case-control	40 people with PD 40 healthy controls	Depression Pain interference	HADS BPI	When compared to the control and groups, the PD group (single) had the highest prevalence of depression, followed by the PD group (married), while the control group (single) had a higher prevalence than the control group (married). A main effect was found on depression severity, but no significant differences were observed between the PD groups. Finally, PD patients (single) had significantly higher pain interference scores than PD patients (married).
Rana et al., 2016 [3]	Observational case-control	74 people with PD 74 healthy controls	Anxiety Depression Severity and frequency of pain Prevalence of Restless Legs Syndrome Sleep quality	HADS BPI RLS diagnostic criteria PSQI	PD patients with pain had significantly higher anxiety severity and worse sleep quality than PD patients without pain. Compared to controls with pain, PD patients with pain had more anxiety, depression and worse sleep quality. PD patients with pain were more likely to report akathisia, tension, and sharp pain compared with controls with pain, but these three pain characteristics did not correlate with

					each other. There were no differences in depression, anxiety or sleep between PD patients with akathisia, tension and acute pain and those without.
Rodriguez-Violante et al., 2016	Cross-sectional observational	341 people with PD	Pain † PD classification SNMs	KPPS UPDRS NMSS	In total, 314 patients were included. Overall, 88.6% of the sample reported at least 1 type of pain. The mean standard KPPS score was 18.8 19.5. Factors associated with higher scores on the KPSS were female gender, treatment with levodopa, presence of depressed mood, exhaustion and dyskinesia. Participants who had the motor subtypes of postural instability and gait difficulty had higher scores on the KPPS compared to those who had other subtypes. Multivariate regression analysis showed that only gender, motor subtype, depressed mood, and NMSQ sleep/fatigue domain scores reached statistical significance as determinants.
Buhmann et al., 2017	Cross-sectional observational	178 people with PD	Anxiety and depression Cognitive function Pain (presence, intensity, duration, location)	HADS MMSE German pain questionnaire Paindetect UPDPQ	Overall, the prevalence of pain was high (95.4%); 91.1% suffered from chronic pain, but only 22.3% of them were diagnosed with a pain disorder. Pain interfered with daily life moderately to very severely in 48.4% of patients and was the most

			PD severity Quality of life	Hoehn -Yahr PDQ-39	distressing symptom in 10.2% of all patients. The pain was mainly located in the back (71.4%) or joints (52.4%), frequently occurring as pain crises (79%), but appearing neuropathic in only 15.3% of patients. Most patients (74.2%) received some type of pain treatment, mainly from orthopedists (62.0%) or general practitioners (50.0%). Physiotherapy (61.3%), analgesics (54.4%) or massage (35.5%) were the most frequent therapeutic measures. Rehabilitation therapy (96.3%) and physiotherapy (89.5%) were rated as more effective, but with very temporary effects. 53.3% of patients attributed PD as the main cause of their pain, but only 33.6% found relief with antiparkinsonian drugs. High levels of pain were associated with higher depression and anxiety scores and lower quality of life.
Choi et al., 2017 [1]	Cross-sectional observational	161 people with PD	Cognitive function Depression PD staging PD symptoms Quality of life Type and intensity of pain	K-MMSE BDI Hoehn -Yahr UPDRS K-PDQ-39 BPI EVA	One hundred and twenty (74.5%) patients with PD had chronic pain. Musculoskeletal pain was the most prevalent type, followed by radicular/neuropathic, dystonic and central pain. PD patients with pain, regardless of the subtype of pain, had

					worse scores on the PDQ-39 than those without pain. Multivariate regression analysis after adjusting for disease-related factors and motor characteristics showed that younger age of onset of PD and high UBDRS, BDI, and VAS scores were significant predictors of poor PDQ-39 scores. Pain, along with depression, poor activities of daily living and younger age at the onset of PD symptoms are associated with poor quality of life. All pain subtypes affect the QoL of PD patients.
Choi et al, 2017 [2]	Cross-sectional observational*	162 people with PD	Depression DMO Pain PD staging Serum levels of calcium and vit. D SMs	BDI DEXA BPI VAS self-report Hoehn-Yahr Blood collection UPDRS	Of the 162 patients with PD, 120 had chronic pain, while 42 did not report pain. The most prevalent type of pain was musculoskeletal, followed by radicular/neuropathic, dystonic and central. PD patients with musculoskeletal pain had lower BMD than PD patients without pain. Multivariate regression analysis showed that low BMD of the lumbar spine, hip and femoral neck was related to advanced age, female sex, low MBI and presence of musculoskeletal pain

Defazio et al., 2017	Multicenter cross-sectional observational	321 people with PD	Motor complications and medical conditions (diabetes mellitus, osteoporosis, rheumatic disease, degenerative joint disease, arthritis and herniated disc) that predispose to pain Pain PD severity SNMs	Clinical and laboratory tests Self-report Hoehn-Yahr NMSS	At the time of the study, 180 PD patients (56%) reported chronic pain, which in most cases was described as muscular or arthralgia pain. The pain preceded the onset of motor signs in 36/180 patients. In the main effect model, factors independently associated with pain were female gender, medical conditions predisposing to pain, Hoehn-Yahr staging, motor complications, and NMS pertaining to sleep/fatigue and mood/cognition. Most of the explanatory variables in the multivariable analysis were similarly distributed in patients whose pain could be related to PD or to a cause other than PD.
Lien et al., 2017	Observational retrospective cohort	490 people with PD 1960 healthy controls	Association with other diseases Pain mechanism Pain part	Data from Taiwan's National Health Insurance Research Database (NHIRD)	A total of 490 patients aged 50 years or older with newly diagnosed PD were identified during a period from 2000 to 2005. Among them, 199 developed MSP after PD. The control group consisted of 1960 participants without PD during the study period randomly selected by corresponding PD cases according to date of PD incidence, age and gender. The study groups were then followed through the end of 2007. Musculoskeletal pain was

					the outcome. MSP incidence rates were higher in the PD group than in the control group. PD was associated with a significantly elevated risk of MSP across all sex and age stratifications, with the highest risk rate observed for middle-aged male patients with PD, followed by older male patients with PD.
Ozturk et al., 2017	Cross-sectional observational	113 people with PD	Anxiety and depression Clinical severity/treatment of the disease Fatigue Pain † PD Internship Quality of life	DSM-IV UPDRS Fatigue Severity Scale VAS Hoehn-Yahr SF-36	Seventy-three patients (64.6%) suffered from chronic pain. Of these, 12 (16.4%) had previous pain at the time of PD diagnosis. The sources of pain experienced by the patients were 89.0% musculoskeletal, 31.5% radicular /peripheral neuropathic, 15.1% dystonic and 4.1% central parkinsonian, respectively. Twenty-six patients (35.6%) had different types of pain simultaneously. The most severe type of pain was central parkinsonian pain. Independent predictors of chronic pain included female gender, UPDRS part II (activities of daily living), UPDRS part III stiffness sub score (motor symptoms), and depression. When compared to individuals without chronic pain, SF-36 scores were lower in patients with chronic pain. Furthermore, the most

					significant factor in the SF-36 was shown to be chronic pain.
Rana et al., 2017	Observational case-control	120 people with PD 120 healthy controls	Depression Pain intensity Pain interference; Pain disability	HADS BPI PDI	The study found a statistically significant direct correlation between the BPI, PDI and PD. A significant direct correlation was also found for depression and pain in PD.
Adewusi et al., 2018	Observational case-control	51 people with PD 51 healthy controls	Pain † Peripheral neuropathic pain Quality of life	KPPS MNSI SF-36	Fifty-one patients and 51 age and sex-matched controls were recruited. The prevalence of global pain was similar in both groups. However, patients with ILD had higher KPPS scores in relation to fluctuating, nocturnal and orofacial domains compared to controls. Patieuts with ILD had more PNP compared to healthy controls. After adjusting for age, gender, duration of illness, and overall KPSS score, the PNP correlated negatively with the physical functioning score, emotional role limitations score, and general health perception score in the SF-36 domains.
Fu et al., 2018	Cross-sectional observational*	144 people with PD	Cognitive function Depression Pain † Quality of life SMS SNMs	MMSE HDRS VAS Location report PDQ-39 UPDRS NMSS	The pain was reported by 75 patients (52.1%), with 49 (65.3%) reporting pain of at least moderate severity. PD patients with pain were older and had longer duration of illness, more severe PD symptoms as assessed by Hoehn-Yahr stage and UPDRS, and higher L-

			Sleep diary Sleep disorders Sleep quality	Epworth Sleepiness Scale Polysomnography Report of use of pharmacological therapy PSQI	dopa equivalent daily dose compared with PD patients without pain. ache. PD patients with pain also had significantly reduced sleep efficiency, increased stage 1 non-rapid eye movement sleep, and decreased rapid eye movement sleep. Binary logistic regression analysis revealed that worse activities of daily living, depressed mood, a higher percentage of N1 sleep and lower sleep efficiency were independent predictors of pain in PD patients.
Galazky et al., 2018	Observational case-control*	97 people with PD 97 neurological patients without the diagnosis of PD and other neuromuscular diseases	Pain intensity Pain radiation Spinal instability	Structured questionnaire X-ray	Low back pain was significantly more frequent in PD (87.6%) compared to controls (62.6%) with longer duration and greater pain intensity. Pain intensity and disability scores were associated with higher PD stages and higher motor scores. Patients with the hypokinetic PD subtype experienced greater pain intensity. Lumbar spine X-rays revealed lumbar arthrosis in 79.6%, scoliosis in 38.8%, and spondylolisthesis in 24.1% of PD patients with low back pain. Scoliosis lateralization and PD symptoms were significantly correlated. Only a small portion of PD patients with low back

					pain received specialized orthopedic treatment.
Ozturk & Kocer 2018	Cross-sectional observational*	168 people with PD 179 healthy controls	Anxiety and depression Fatigue Disease severity Pain intensity Physical activity SMs	HADS Severe fatigue scale Hohen-Yahr VAS +3x 60 min/week self-report UPDRS	The frequency of chronic low back pain in patients with Parkinson's disease and controls was 48.2% and 26.7%, respectively. Risk factors predictive of chronic low back pain in Parkinson's disease were general factors including age and HADS - depression sub score and DP - related factors including stiffness and posture item scores.
Rana et al., 2018 [1]	Observational case-control	100 people with PD 100 healthy controls	Anxiety Depression Pain intensity Pain interference Prevalence of Restless Legs Syndrome Sleep quality	HADS BPI RLS diagnostic criteria PSQI	PD patients with poor sleep quality had greater pain severity and pain interference than controls and PD patients with good or borderline sleep quality. PD patients with poor sleep quality also had a higher frequency and severity of depression and anxiety. However, patients with right-sided onset of PD were not significantly correlated with depression, anxiety or pain.
Rana et al., 2018 [2]	Observational case-control	96 people with PD 96 healthy controls	Depression Pain intensity Pain interference	HADS-D BPI	It was determined that PD patients had significantly higher pain severity scores compared to controls. PD patients with depressive symptoms had significantly higher pain intensity and pain interference scores than controls without depressive symptoms. Patients

					with PD reported higher scores on the global pain interference of the BPI and all components of the pain interference subscale.
Rana et al., 2018 [3]	Observational case-control	34 people with PD 34 people with PD+AO 34 people with AO 34 controls	Anxiety Depression Pain intensity Pain interference	HADS BPI	Patients with PD+AO and PD had worse depression severity and were more likely to report anxiety and depression than patients with MAS. Patients with PD+OA were more likely to complain of paresthetic and akathisic pain, but less likely to complain of pain compared to patients with PD and patients with OA. PD+OA patients were more likely to have greater pain intensity and were more likely to report sharp, radiating pain than patients with right-sided onset of PD. Patients with PD+OA were also more likely to report more depression than patients with right-sided onset of PD.
Scalzo et al., 2018	Cross-sectional observational	45 people with PD	Cognition Depression Fatigue Pain † PD severity SMs Sleep disorders	M MSE BDI PFS-16 McGill Questionnaire EVN Hoehn-Yahr UPDRS PDSS	Forty-five patients participated in the study, of which 19 (42.2%) complained of pain, most of them after the diagnosis of PD (74%). There was no difference between the groups with and without pain for the evaluated clinical parameters, with the exception of fatigue, which was more prevalent and more severe in patients with pain.

Silva et al., 2018	Cross-sectional observational	77 people with PD	Daytime squeaking /squeaking Pain † Uncomfortable/ unusual biting Tinnitus Morning Stiffness Click PD severity	Self-report Research Diagnostic Criteria for Temporomandibular Disorders Hoehn-Yahr	139 people with Parkinson's disease were evaluated. Of these, 77 met the eligibility criteria, with 70% of the sample being male , with a mean age of 62±9 years, time since diagnosis of Parkinson's disease of 6±4 years and with 71% of the sample in the moderate stage. No significant associations were found between age, sex, time and stage of the disease with temporomandibular disorders. Of the analyzed variables, the significant results showed that the presence of pain represents a greater chance of developing temporomandibular dysfunction, crepitus reflects a moderate accuracy in the classification of the temporomandibular joint disorder, and clicking increases the probability of having temporomandibular dysfunction.
Silverdale et al., 2018	Multicenter cross-sectional observational	1957 people with PD	Anxiety and depression Autonomic symptoms Characteristics and intensity of pain Cognitive function Neuropathic pain	Leeds Anxiety and Depression Scale PD Outcome Scale - Autonomic Symptoms SFMPQ VAS KPPS MoCA LANSS	85% of participants reported pain (42% with moderate to severe pain). The pain influenced the quality of life more than motor symptoms in a multiple regression model. Factors predicting overall pain severity included affective symptoms, autonomic symptoms, motor complications, female gender and

			Quality of life SMs and SNMs	EQ-5D UPDRS	younger age, but not motor impairment or disease duration. There was a negligible correlation between the severity of motor impairment and the severity of pain musculoskeletal or dystonic pain, as well as between the severity of *Off* period motor problems and the severity of Off period *pain* or *Off* period dystonic pain. Features of central sensitization including allodynia and altered pain sensation were common in this population. The use of drugs directed at central pain was very low.
Suzuki et al., 2018	Observational case - multicentric control	436 people with PD 401 healthy controls	Sleep disorders Disease severity Habits, education, sleep state and headaches Pain intensity Mental disorders Migraine	PDSS-2 ESS Sleep Behavior Disorder Screening Questionnaire PSQI Hoehn-Yahr Structured questionnaire† VAS Semi-structured Neuropsychiatric Mini Interview International Semi-structured questionnaire †	Patients with PD had lower lifetime and 1-year migraine prevalence than controls. However, lifetime and 1-year prevalence of headaches did not differ between PD patients and controls. After adjusting for sex, timing of assessment of headache changes, and recovery period, PD patients with headaches or migraines exhibited a pronounced reduction in the intensity, frequency, and overall severity of their headaches and migraines after the onset of PD compared with controls with headaches or migraines. PD patients with migraines exhibited a higher rate of depression and higher

			SMs	UPDRS	PSQI scores than those without headaches.
Zella et al., 2018	Cross-sectional observational*	2814 people with PD	Pain characteristics	Structured questionnaire	1610 male patients. Spinal paravertebral pain emerged as the dominant form of pain. A significant correlation was also demonstrated between gender and location of pain, pain intensity and pain as impairment of quality of life. Nonsteroidal anti-inflammatory drugs were the analgesics most used by patients. Other than non-opioid analgesics, no significant correlation was demonstrated between pain treatments and gender.
Alwardat et al., 2019 [1]	Cross-sectional observational	48 people with PD	Cognitive function Pain † PD severity PD staging The specific function of the back	MMSE BPI Hoehn -Yahr UPDRS ODI	Groups had significantly worse ODI disability, BPI pain, and higher LEDD and Hoehn-Yahr stage than the DP groups. However, no differences were found in the duration of PD and UPDRS in the same groups. Furthermore, no differences were observed between the PS and C&A groups in the mentioned scales.
Alwardat et al., 2019 [2]	Cross-sectional observational	45 people with PD	Cognitive function Neck pain Pain † PD staging PD severity	MMSE Neck Disability Index BPI UPDRS Hoehn -Yahr	The PD group compared with the PS and C&A groups showed differences in NDI, BPI-MAS, BPI-PI, LEDD and Hoehn-Yahr staging, but no differences were found in the duration of PD, UPDRS-II and III in the same

					groups. Furthermore, no differences were observed between the PS and C&A groups in the mentioned scales.
De Mattos et al., 2019	Cross-sectional observational	54 people with PD	Balance Gait Pain † SMS	Mini -BESTest Dynamic Gait Index BPI KPPS UPDRS	Thirty-eight participants (70.3%) reported mild to moderate pain. A positive correlation was found between total KPPS score and performance on general UPDRS II activities; a negative correlation was found between BPI pain intensity and UPDRS III motor function; and a negative correlation was found between the BPI pain intensity and the UPDRS III bradykinesia subscore. There was no correlation between pain and gait or balance performance. Musculoskeletal pain was the predominant type (in 81,5% of individuals), followed by night pain (52,6%) and pain related to floating (47,3%). The most painful areas were lower limbs (33,0%) and shoulders/cervical region (31,0%). Twenty-one of the 38 participants (55,3%) reported pain interfering with their ability to work and gait and general activities.
Hirsi et al., 2019	Cross-sectional observational	103 people with PD	Depression Pain †	Patient Health Questionaire-9 KPPS	We surveyed 103 patients with PD. Of these, 87 (84%) had pain symptoms. Only 16 (18.4%) received pain

					medication, and no one was referred to physical therapy.
Joseph et al., 2019	Cross-sectional observational	100 people with PD 47 healthy controls	Balance Cognitive function Depression Disease severity Pain † Quality of life SMs	Mini -BESTest MMSE Geriatric depression Scale 20 Hoehn-Yahr Domain of the SF-36 PDQ-39 UPDRS	Pain severity was significantly higher in people with Parkinson's disease than healthy in controls. Among people with Parkinson's disease, the multivariate predictor model, identified three independently associated factors explaining 34% of the variation in pain severity scores. Worse balance performance, shorter illness duration, and worse health-related quality of life were independently associated with pain severity. Pain severity is greater in those living with PD than in controls, and severity appears to be associated with disease characteristics and overall health.
Martinez-Martin et al., 2019	Multicenter cross-sectional observational	300 people with PD	Anxiety and depression Disease severity Pain † Quality of life	HADS Hoehn -Yahr Clinical Severity Impression Index for PD VAS KPPS KPPQ EQ-5D-3L PDQ-8	According to the PDSS-2, 99.3% of our sample suffered from at least one sleep problem. Those who reported experiencing any form of pain suffered significantly more from sleep disturbances than those who did not. The PDSS-2 showed moderate to high correlations with the KPPS, KPPQ and EVA. When PDSS-2 items 10 to 12 (related to pain) were excluded, the correlation values decreased, whereas

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			SMs SNMs Sleep disorders	Scales for Outcomes in Parkinson's Disease-Motor NMSS PDSS-2	these items showed moderate to high correlations with KPPS, KPPQ and VAS. Among the analyzed variables, multiple linear regression models suggested that KPPS and KPPQ were the most relevant predictors of sleep disorders (according to the PDSS-2), although after excluding the pain items from the PDSS-2, depression was the relevant predictor. Depression and anxiety were the most relevant predictors in the analysis involving the VAS-Pain. Regression analysis, considering only the KPPS domains, showed that nocturnal and musculoskeletal pain were the best predictors of general nocturnal sleep disturbance.
Rana et al., 2019	Observational case-control*	88 people with PD 88 healthy controls	Depression sleep disorders Pain †	HADS PSQI BPI PDI	Indian PD did not differ from Caucasian PD in anxiety or depression. However, Caucasians with PD were more likely to report painful pain by 80 times and dull pain by 108 times compared to Indians with PD. Indians with PD were 82% less likely to have pain interfering with social activities and 90% less likely to have pain interfering with relationships with others compared to Caucasians with PD.

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Vila-Chã et al., 2019 [1]	Cross-sectional observational	229 people with PD	Anxiety and depression Pain† PD severity SMs Sleep disorders	HADS Questionnaire† Hoehn -Yarh UPDRS PDSS-2	Seventy-five (33%) patients had clinically relevant sleep disturbance (PDSS-2≥18) and 162 patients (71%) reported pain. Of those with pain, 38 (24%) had central parkinsonian pain. PD patients with sleep disorders had more pain and more severe motor symptoms, less functional independence, more symptoms of anxiety and depression and worse quality of life. Among patients with pain, central parkinsonian pain was the pain subtype with the highest chance of sleep disturbances, even taking into account motor symptoms (Hoehn-Yarh *off*), motor fluctuations, pain intensity (BPI) and symptoms of anxiety and depression (HADS).
Vila- Chã et al., 2019 [2]	Cross-sectional observational	292 people with PD	Anxiety and depression Dopamine dysregulation syndrome Freeze Gait Pain † PD severity *On* and *Off* Status	HADS Short-chain Impulsive Compulsive Disorders Questionnaire in PD FOG-Q BPI PDI Hoehn-Yahr Structured questionnaire†	Two hundred and twelve patients (73%) reported pain, which was classified as musculoskeletal (63%), related to dystonia (27%), central parkinsonian (22%) and/or radicular or neuropathic (9%). Patients with pain had more comorbidities and more severe motor symptoms. Patients with central parkinsonian pain were significantly younger, had earlier disease onset, fewer comorbidities, greater severity of non-axial motor

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			SMs	Schwab and England Independence Scale UPDRS	symptoms, more pain-related disability, and more pain relief with antiparkinsonian medication than patients with non-axial parkinsonian pain central.
Cruz-Almeida et al., 2020	Cross-sectional observational*	113 people with PD 60 controls	Cognitive phenotypes Depression PD comorbidity Pain intensity Pain interference	Executive functions and episodic memory measures WAIS-III Letter Number Sequence and Digit Symbol Tests Stroop Color-Word Test word-color test Trail Making Test Part B Hopkins Verbal Learning Test Revised recognition and delay discrimination measures WMS-III Logical Memory Delay Recovery Geriatric Depression Scale Charlson comorbidity scale BPI	PD participants with low executive function reported significantly greater pain interference despite reporting similar levels of pain severity compared to other phenotypes. These differences remained statistically significant even after accounting for important confounders such as anxiety and depression.

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			SMs	UPDRS	
Faccio et al., 2020	Cross-sectional observational	81 people with PD	Chronic pain † Depression DTM Nonspecific physical symptoms	Classification of chronic pain based on the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD)	A total of 81 seniors met the eligibility criteria – 67% were male, 74% were married or had a partner, 43% reported earning 1 to 2 minimum wages and 47% were in the moderate stage of PD. The TMD was identified in 22% of the sample, with 12% reporting chronic pain. Statistical analysis showed an association between TMD and chronic pain and between TMD and moderate to severe depression.
Florin et al., 2020	Cross-sectional observational*	20 people with PD	Depression Insanity Temporal summation Thermal latency of pain Thermal pain tolerance SMS	BDI Mattis Dementia Rating Scale VAS KPPS PainDETECT Contact termode Modified ladder method with verbal feedback UPDRS	Levodopa increased endogenous pain inhibition in terms of perceived pain intensity and unpleasantness compared to an off-medication state. Greater clinical pain was associated with greater increases in pain inhibition. Levodopa did not affect heat pain threshold, tolerance or temporal summation.
Geroin et al., 2020	Cross-sectional observational	283 people with PD	Degree of trunk flexion Limitation in ADLs and SMs	Wall goniometer Software Based Measurements (SBM) with Kinovea freeware program UPDRS	We found significant associations between Hoehn-Yahr stage modified, disease duration, sex and limitation in ADLs, motor impairment, back pain intensity and history of falls. The degree of trunk flexion was associated only with motor impairment in lateral

			Pain	END	trunk flexion. The receiver's operating characteristics curves showed that patients with lateral trunk flexion of 10.5° may have moderate/severe motor impairment.
Ghosh et al., 2020	Cross-sectional observational	167 people with PD	Depression Pain † PD severity SMS SNMs, dysautonomia and specific aspects of sleep quality	BDI BPI KPPS Hoehn-Yahr UPDRS NMSS	The pain prevalence was 88,6%, not correlated with age, motor severity (UPDRS part III) or disease duration, while a weak correlation with female sex and Hoehn-Yahr stage >2,5 was found. Multiple NMS correlated significantly with pain. Specifically, sleep disturbance had the strongest correlation with pain, followed by depression, gastrointestinal and cardiovascular disorders. Further analyzes showed that sleep and cardiovascular disorders were independently associated with pain and that these symptoms clustered in a subset of PD patients. The relationship between pain, sleep and dysautonomia persisted regardless of dopamine replacement therapy.
Gonçalves et al., 2020	Cross-sectional observational	123 people with PD	Demographic data pain intensity	Structured questionnaire VAS	One hundred twenty-three patients with a mean age of 68,1±11,8 years and mean disease duration of 7,0±4,9 years answered the questionnaire. The pain was reported by 102 (82,9%) patients: 71 (57,7%) with low back

					pain and 31 (25,2%) with pain in other body segments. There was no difference regarding age, education, duration of symptoms and diagnosis of Parkinson's disease when comparing individuals with and without pain, as well as individuals with pain in other regions and low back pain. The group with low back pain complained of pain in a greater number of body segments besides the lumbar region, with a longer duration of this symptom and more frequent use of analgesics. Among individuals in the group with low back pain, women had greater pain intensity.
Kobylecki et al., 2020	Cross-sectional observational*	1909 people with PD	Impulsive disease control Neuropathic and nociceptive pain Pain intensity	Questionnaire for Impulsive-Compulsive Disorders in PD LANSS VAS KPPS McGill's Questionnaire	Most patients reported pain, which was classified 76,6% as nociceptive, while 8,3% had neuropathic pain. ICB was reported by 25% of the population. The equivalent dose of levodopa was higher in participants with any ICB compared to those without. Participants with any ICB scored higher on all pain scales and were more likely to have high pain and neuropathic pain.
Nguy , 2020	Cross-sectional observational	52 people with PD	Anxiety and depression PD severity	HADS UPDRS	Univariate regression analyzes showed that increased disease severity, longer disease duration, greater central

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			Pain intensity Pain interference Physical activity Sleep quality Central sensitization	KPPS BPI Incidental and Planned Exercise Questionnaire PSQI Central Sensitization Inventory	sensitization, increased physical activity, poor sleep, anxiety, and depression were associated with worse pain on one or more pain measures. Multivariate regression models accounted for 56% of the KPPS variance, 25% of pain severity, and 36% of pain interference. Poor sleep independently contributed to worse pain scores in all models.
Rocha-Filho & Souza-Lima, 2020	Cross-sectional observational	46 people with PD	Anxiety and depression Pain † neck stiffness†	HADS Structured questionnaire	About 46 patients were included, 52% were men, mean age was 66 ± 11 years. Forty-three patients had headaches, 12 (26%) had migraines, 31 (67%) had tension-type headaches. We found no association between headache frequency or intensity and different stages of PD. There was no correlation between the UPDRS score and the intensity or frequency of headaches. No association was found between the degree of neck stiffness and headache frequency or intensity. Twelve patients said their headaches started after their PD diagnosis. There was no difference in frequency and characteristics of headaches and PD characteristics between these patients and the other patients with previous headaches.

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Silveira Barezania et al., 2020	Cross-sectional observational	115 people with PD	Ability to contract the transversus abdominis Cognitive function Depression Disability-related to low back pain in PD Epidemiological characteristics PD severity Quantitative measures of clinical low back pain Quality of life SMs	Prone test with the sphygmomanometer MMSE BDI Roland Morris Disability Questionnaire Epidemiological questionnaire Hoehn-Yahr McGill 's Questionnaire PDQ-39 UPDRS	One hundred and fifteen patients answered the questionnaire and 95 (82.6%) reported painful symptoms. Of these, 67 (58.3%) had chronic low back pain and approximately 40% of the patients reported its onset before the diagnosis of PD. Higher pain intensity scores, depressive symptoms and UPDRS II and III, more advanced stages of PD and absence of TrA contraction determined the functional limitation induced by low back pain. However, pain intensity (McGill), PD symptom severity (UPDRS III) and absence of TrA contraction were identified as predictive factors of functional limitation and explained 66.1% of the RMDQ variance. Pain intensity and disability related to low back pain had a negative impact on quality of life.
Sung et al., 2020	Cross-sectional observational	25 people with PD	Affection Depression Dependent oxygen level in regional blood Drug development Induced	PANS Geriatric Depression Scale phasic pressure WOQ-9 MAIMS	Dyskinetic PD participants experienced increased sensitivity to pressure pain. This was associated with increased pressure-induced pain, innocuous BOLD activity in areas associated with pain intensity coding, spatial pain orientation, descending pain mediation, sensorimotor integration, and motor control.

			fluctuations and dyskinesia Severity of PD Pain intensity Pain ratings Presence of clinical pain † Pressure pain threshold Quality of life	 UPDRS NPS Functional MRI SFMPQ LDP PDQ-39 PDY-26	Levodopa reduced pressure pain ratings and improved negative affect, although it did not affect BOLD activity differently between groups.
Walmsley et al., 2020	Cross-sectional observational	120 people with PD 76 physiotherapists	Demographic data History of PD Shoulder disorders and pain Knowledge of physiotherapists on the management of disorders and pain in the shoulder of people with PD	Structured questionnaire	A postal survey was sent to 189 PD patients and an online survey was emailed to 336 physical therapists. A response rate of 63% was obtained for PD patients and 23% for physical therapists. Of patients with PD, 13% reported onset of shoulder pain and/or stiffness within 5 years of diagnosis, with no past history of shoulder problems. Of these patients, 8% specifically reported shoulder symptoms as the initial manifestation of the disease. However, 74% of the surveyed physiotherapists were unaware of the potential for early onset of this symptom.
Yilmaz et al., 2020	Cross-sectional observational*	110 people with PD	Disease severity Freeze Gait Pain intensity	Hoehn-Yarh FOG-Q VAS	Fifty-eight of the patients experienced FOG and 43 experienced falls. Among the patients, 42 had no pain, while 35

			SMs	UPDRS	had pain in the lower limbs. Higher UPDRS and FOG motor scores and advanced disease were seen in significantly more patients with FOG and fall. VAS scores were not affected by the presence of FOG or fall. There was a positive correlation between FOG severity and VAS score in male patients. More patients with falls had pain in the lower limbs than those without falls.
Agrawal et al., 2021	Cross-sectional observational	100 people with PD	Pain † Quality of life Stage and severity of PD	KPPS PDQ-8 UPDRS	The prevalence of different types of pain in PD patients was 70%, including mainly musculoskeletal (53%), buoyancy-related (35%) and night pain (27%). Individuals with pain developed PD symptoms at a younger age and had a longer duration of illness. A positive correlation was found between KPPS scores and UPDRS parts III and V, while a negative correlation was observed with UPDRS part VI. Pain in individuals with PD had a significant impact on QoL.
Kinugawa et al., 2021	Cross-sectional observational	24 people with PD	Electroencephalography Pain †	International system of 10-20 electrode placement and a sampling rate of 200 Hz UPDRS	Twenty-four patients with sporadic PD were assessed for the presence of pain. Time-frequency and coherence analyzes were performed on their EEG data. Total and regional brain

					coherence was calculated and compared between patients with positive and negative pain. There was no significant difference in whole brain coherence between pain-positive and pain-negative groups. However, temporal-temporal coherence differed significantly between the two groups. Our findings indicate that aberrant synchronization of intertemporal regions is involved in PD-related pain.
Kurihara et al., 2021	Retrospective cross-sectional observational	31 people with PD	Cognitive function Depression PD severity Quality of life SMs Wear	Girl MMSE Zung 's Depression Self-Rating Scale Hoehn-Yarh PDQ-8 UPDRS WOQ-9	In this study, 331 patients with PD were classified into three groups: no pain group (67,4%), non-fluctuating pain group (22,1%) and fluctuating pain group (10,6%). We evaluated the patients ' history and its impact on the QoL of each group. The group with pain had higher levels of depression, a higher frequency of visual hallucinations and lower QoL compared to the group without pain. The fluctuating pain group had a younger onset, a higher Hoehn-Yahr stage, and a higher frequency of attrition and dyskinesia than the other groups. We compared the PDQ-8 summary score in each pain group with the no-pain group using an analysis of variance. As a result, the

					PDQ-8 was significantly higher in both non-fluctuating and fluctuating pain groups.
Liguori et al., 2021	Cross-sectional observational	26 people with PD	Anxiety Cognitive functioning Daily drowsiness Depression Fatigue Functional assessment Mild Cognitive Impairment Neuropsychological battery Pain † SMS	Parkinson's Anxiety Scale MoCA ESS BDI Parkinson's Fatigue Severity Scale 10-meter walking test tug G -walk Line Orientation Judgment Test Movement Disorders Society Task Force Tier II A-test performance test Modified card sorting test Evocation test in prose Rey's Auditory Verbal Learning Test copy of drawings KPPS UPDRS	Fatigue had a moderate negative correlation with step cadence and a moderate to strong positive correlation with gait duration, TUG, and TUG Dual Task. Pain showed a moderate positive correlation with walking duration. Twelve patients had mild cognitive impairment and reported significantly worse scores on gait duration, pain, and fatigue. According to cognitive z-scores, the group with mild cognitive impairment showed a moderate negative correlation between visuospatial skills and fatigue.
Lopes et al., 2021	Observational case-control	34 people with PD	Pain intensity PD severity	NPS Hoehn-Yahr	Mean pain intensity among those using medication (2,17±0,39) was

					significantly lower than in the abstinence group (4,2±0,59), which corresponded to an increase in the total staging score functional from 93 to 111, respectively.
Naisby et al., 2021	Cross-sectional observational*	154 people with PD 99 controls	Cognitive function Depression Pain † PD severity SMs	MMSE MoCA Geriatric Depression Scale NMSQ Pain domain of PDQ-39 Hoehn -Yahr UPDRS	Unexplained pain was common in the PD group and occurred more frequently than in age-matched controls. 'Aches and pains' occurred more frequently than 'muscle cramps and spasms' at every time point except 54 months.
O'Neill et al., 2021	Cross-sectional observational	1916 people with PD	Depression Pain † SMs	Leeds Anxiety and Depression Scale KPPS EVE McGill 's Questionnaire LANSS UPDRS	A total of 139 (7,3%) patients reported the presence of some form of orofacial pain. Burning mouth syndrome was reported in 32 (1,7%), while chewing was found in 38 (2,0%) and chewing in 78 (4,0%). Orofacial pain was significantly more common in females (10,4%) than in males (5,9%). Multiple logistic regression analysis showed a significant association between orofacial pain and pain intensity, neuropathic pain, and oral and non-motor motor dysfunction.
Paul et al., 2021	Cross-sectional observational	127 people with PD	Diagnosing Restless Legs Syndrome	Restless Legs Syndrome Diagnostic Criteria	The results demonstrated that the patient with Parkinson's disease who reported pain scored 23 points higher for RLS prevalence and 8,5 points

			Pain † Pain interference Pain perception	Semi-structured interview BPI	higher for RLS severity compared to the group of patients with PD who denied pain.
Prell et al., 2021	Cross-sectional observational*	52 people with PD	Coping with pain Cognitive function Depression Pain classification Quality of life Symptoms	Coping Strategy questionnaire MoCA BDI Pain domain of the SF-36 SF-36 Hoehn -Yahr NMSQ UPDRS	Most patients deal with pain through active cognitive strategies (self-copying statements) and active behavioral strategies (increasing pain behaviors and increasing activity levels). Active coping was associated with lower pain scores. Regarding the QoL domains, active coping was associated with better physical functioning and better energy, while passive coping was associated with worse emotional well-being. However, as demonstrated by MANOVA, the impact of coping factors (active and passive) on the SF-36 domains was insignificant after correcting for age, motor function and depression
Vila-Chã et al., 2021	Cross-sectional observational	260 people with PD	Impulse control disorders, other compulsive behaviors, and compulsive medication use Pain classification Symptoms	Questionnaire for Impulse Control Disorders in the Short Form of Parkinson's Disease Ford rating UPDRS	One hundred and eighty-eight patients (68%) reported pain; and in 41 (22%) of them, the pain was classified as central parkinsonian pain. PD patients with central parkinsonian pain had a better cognitive performance on the Initiation/Perseveration and Conceptualization subscales of the Impulse Control Disorders in the Short

					Form of Parkinson's Disease Questionnaire, but reported more other compulsive behaviors and had more current smoking habits than those with no pain or no central parkinsonian pain. Only patients with pain, regardless of type, had gambling disorders.
Gao et al., 2022	Cross-sectional observational	88 people with PD	Anxiety Cognitive function Daily life activities Depression Pain † PD severity Sleep quality SMs	HAMA MMSE Scale of activities of daily living HAMD KPPS VAS Hoehn-Yahr PSQI UPDRS	The prevalence of sleep disorders was 76.1% in patients with PD-related pain. Among these patients, the poor sleep group had more severe motor symptoms, more anxiety and depression symptoms, less functional independence, and more pain, such as musculoskeletal pain, chronic pain, floating-related pain, night pain, and discoloration/edema/edema. In addition, PSQI scores correlated positively with scores on all 7 KPPS domains. Hoehn-Yahr stage and PSQI were significant independent variables explaining 50.0% of the variance in KPPS scores.
Gültekin et al., 2022	Observational retrospective case- control	55 people with PD 20 healthy controls	ADLs Depression Fatigue	Scale of activities of daily living BDI Fatigue severity scale	We found that MMST and ROM values of flexion and extension were significantly decreased in the patient group compared to controls. Hoehn-Yahr stage, UPDRS, Roland Morris Disability Questionnaire, ODI, and

			Functional status and disability PD disability PD severity Pain intensity Spine mobility	Roland Morris Disability Questionnaire ODI UPDRS Hoehn-Yalu VAS Modified-Modified Schober Test Range of motion in lumbar flexion and extension	VAS scores were higher and MMST scores were lower in patients with low back pain than in patients without low back pain. In the multivariate analysis, the presence of low back pain did not correlate with any of the parameters, including age, sex, disease duration, dominant symptom, ADL, depression and fatigue severity.
Kinugawa et al., 2022	Cross-sectional observational*	24 people with PD	Cognitive function Pain intensity SMs	MMSE NPS SFMPQ UPDRS MRI	We evaluated 23 patients with sporadic PD based on functional magnetic resonance imaging and pain intensity using the SFMPQ reviewed. PD patients had higher pain intensity scores in the "*Off*" state than in the "*On*" state. Pain intensity in the "*Off*" state was substantially correlated with functional connectivity between the nucleus accumbens and the primary motor/sensorial cortices and the contralateral nucleus accumbens. Changes in pain intensity from the "*On*" state to the "*Off*" state exhibited correlations with those between the nucleus accumbens right and nucleus accumbens left and right precentral

					gyrus / right insular cortex from the "*Off*" to the "*Off*" state. nucleus accumbens aberrant bilateral and nucleus accumbens right– right precentral gyrus / right insular cortex functional connectivity in the "*Off*" state were closely related to the pain symptoms developed from the "*On*" to "*Off*" states.
Li et al., 20 22	Cross-sectional observational	452 people with PD	Anxiety Depression Duration and location of pain Pain intensity Sleep quality Quality of life	HAMA HAMD Self-report Ford rating NPS PDSS PDQ-39	Two hundred and six patients (45,58%) reported musculoskeletal pain, usually in the lower limbs and back. Levodopa resulted in a 30% reduction in pain intensity scores in 170 subjects. Female gender and daily doses equivalent to levodopa were associated with an increased risk of musculoskeletal pain. Pain duration, motor symptoms and depression were significantly associated with quality of life.
Samanci et al., 2022	Retrospective cross-sectional observational	86 people with PD	NMSs, date of onset, pain complaints, type of pain and site of pain	Self-report Ford rating	Eighty-six patients were included (42 women, 44 men). The first complaints were bradykinesia, tremor, tremor and bradykinesia, shoulder pain, tremor and painful cramps. These complaints started 10.1±5.22 years ago and the diagnosis of PD was made on average 8.56±4.87 years ago. The first specialized departments to which

					patients with these complaints applied were Neurology (n=34), Physiotherapy and Rehabilitation (n=34), Neurosurgery (n=10) and Orthopedics (n=8). The first admission in Neurology was 8.7±4.85 years ago. Pain complaints started 7.2±6.69 years before the first hospitalization in 56 patients. Musculoskeletal pain was 86%, dystonic pain was 25%, central pain and neuropathic pain were 11% each in the group of patients who experienced pain.
Sung & Kang, 2022	Cross-sectional observational*	236 people with PD 42 people with multiple system atrophy 31 Progressive supranuclear palsy 38 vascular parkinsonism	Central or primary pain Cognitive function Depression PD severity Pain severity Pain part Type of pain SMs	Definition based on the literature K-MMSE BDI Hoehn-Yahr VAS Self-report Ford rating UPDRS	No difference was observed in the presence of pain, severity or type between the four groups. However, the temporal relationship between pain and motor symptoms differed. Pain preceded motor symptoms in PD, progressive supranuclear palsy, and vascular parkinsonism, but often followed motor symptoms in PSP. The location of pain in the body was different among the four patient groups, and leg involvement was more common in PSP.

*Study types based on authors' opinion (EOM and MIOD) due to this information being absent, ambiguous or incomplete in the cited study; † Variables and instruments as indicated by the authors of the included studies, but without correspondence with the gold standard instrument recognized in the literature.

ADL's: Activities of Daily Living; BDI: Beck Depression Inventory; BPI: Brief Pain Inventory; C&A: Camptocormia and Antecollis; DASS: Depression Anxiety and Stress Scale; DEXA: Dual Energy X-Ray Absorptiometry; DMS-III: Diagnostic and Statistical Manual of Mental Disorders; PD: Parkinson's disease; NPS: Numerical Pain Scale; ESS: Epworth Sleepiness Scale; VAS: Visual Analog Scale; VNS: Visual Numerical Scale; FACS: Facial Action Coding System; FOG-Q: Gait Freezing Questionnaire; HADS: Hospital Anxiety and Depression Scale; HAMA: Hamilton Anxiety Rating Scale; HAND: Hamilton Depression Rating Scale; K-MMSE: Korean Version of the Mini-Mental State Examination; K-PDQ-39: Korean Version of the Parkinson's Disease Questionnaire; KPPS: King Parkinson's Disease Pain Scale; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs; PPT: Pressure Pain Threshold; LEED: Levodopa Equivalent Dose. MA: Major Depression; MADRS: Montgomery-Åsberg Depression Rating Scale ; MAIMS: Modified Abnormal Involuntary Movement Scale; MI: Minor Depression; MMSE: Mini Mental State Examination; MNSI: Michigan Neuropathy Screening Tool; MoCA : Montreal Cognitive Assessment Beijing Version; NFR: Nociceptive Flexion Reflex; NHP: Nottingham Health Profile; NMSQT: Non-Motor Symptoms Questionnaire; NMSS: Non-Motor Symptom Scale; NO: No Depression; NWDS: Northwestern Disability Scale ; ODI: Oswestry Disability Index ; PACA: Assessment of Palliative Care; PANAS: Positive and Negative Affect Timeline; PDI: Pain Disability Index ; PDQ-39: Parkinson's Disease Questionnaire; PDQ-8: Parkinson's Disease Questionnaire with eight dimensions; PDSS: Parkinson's Disease Sleep Scale; PDYS-26: 26-item Parkinson's Disease Dyskinesia Scale; PFS-16: Parkinson's Disease Fatigue Scale; PS: Pisa Syndrome; PSE: Present State Examination; PSQI: Pittsburg Sleep Quality Index; Heat Pain Threshold; HRQL: Health-Related Quality of Life; FMR: Functional Magnetic Resonance; SF-36: Medical Outcomes Study 36—Item Summary Form; SFMPQ: McGill Pain Questionnaire - Short Form; SMs : Motor Symptoms; NMSs : Non-Motor Symptoms; RLS: Restless Legs Syndrome; SQ: Sleep Questionnaire; TUG: Timed UP and Go test; UPDRS: Unified Parkinson's Disease Rating Scale; WAIS-III: Wechsler Adult Intelligence Scale; WMS-III: Wechsler Memory Scale ; WOQ-9: Wear Questionnaire-9; WS: Sensation of Heat:

Table 3 - Pain criteria presented from the studies

Author, date	Chronology of pain		Origin of pain		Type of pain mechanism			Terminology reported in inclusion criteria	Terminology reported in the results
	Acute	Chronic	Primary	Secondary	Neuropathic	Nociceptive	Nociplastic		
Indo, et al., 1983	NR	NR	NR	NR	NR	NR	NR	NR	NR
Starkstein et al., 1991	NR	NR	NR	NR	NR	NR	NR	NR	NR
Djaldetti et al., 2004	NR	NR	NR	NR	NR	NR	NR	NR	NR
Quittenbaum & Grahn, 2004	NR	NR	NR	NR	NR	NR	NR	NR	NR
Giuffrida et al., 2005	NR	NR	NR	NR	NR	NR	NR	NR	The pains were classified as osteoligament (rheumatologic), muscular, neurogenic, headache, visceral pain, syndrome without resting legs, acatisia or varies. Wall and Melzack classification (1984) was also used
Lee et al., 2006	NR	NR	NR	NR	X	X	NR	NR	a) Neuropathic or nociceptive pain b) A new general classification of pain based on a model used in the treatment of cancer: PAIN related to IPD; pain related to the treatment of ID (i.e., PAIN-causing DPI drugs); Pain indirectly related to IPD (e.g., pressure ulcers/injury from falls); Pain not related to ID; other/multiple causes
Tinazzi et al., 2006	NR	NR	NR	NR	NR	NR	NR	NR	Ford Classification
Broetz et al., 2007	NR	NR	NR	NR	NR	NR	NR	NR	Root pain: projection of leg pain, numbness or weakness in the region where the pain was projected
Defazio et al., 2008	NR	NR	NR	NR	NR	NR	NR	NR	Information on any pain present at the time of the study and lasting at least 3 months was recorded. Pain associated with visible dystonia was

									defined as dystonic pain, while non-dystonic pain was classified as colic (muscle pain), arthritic (stiffness after rest and pain at movement, confined to joints), peripheral neuropathic pain (pain in the territory of a root or nerve) and central neuropathic pain (burning or tingling)
Silva, et al., 2008	NR	NR	NR	NR	NR	NR	NR	NR	Ford Classification
Beiske et al., 2009	NR	NR	NR	NR	NR	NR	NR	NR	It characterized the qualities of pain (burning, dull, sore, tension, tightening or irradiation), the onset of pain (creeping or acute) and its fluctuation, location and precipitating/relievin g factors. Based on this information and clinical examination,

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									each reported pain was categorized as musculoskeletal pain, root/neuropathic pain, dystonic pain or CNP
Ehrt et al., 2009	NR	NR	NR	NR	NR	NR	NR	NR	NR
Polidorio et al., 2009	NR	NR	NR	NR	NR	NR	NR	NR	NR
Roh et al., 2009	NR	NR	NR	NR	NR	NR	NR	NR	NR
McNamara et al., 2010	NR	NR	NR	NR	NR	NR	NR	NR	NR
Müller, et al., 2011	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mylius et al., 2011	X	X	NR	NR	NR	NR	NR	In the group of pd patients, only pd-related clinical pain was allowed	Acute and chronic pain related to PD was assessed by a small questionnaire and classified into 5 forms according to Ford
Skogar et al., 2012	NR	X	NR	NR	NR	NR	NR	Chronic pain was defined as the occurrence of PD-related pain for three days or more per week for at least	NR

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								three months immediately prior to inclusion in the study	
Rana et al., 2013[1]	NR	NR	NR	NR	NR	NR	NR	NR	Ford Classification
Rana et al., 2013[2]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Coriolano et al., 2014	NR	NR	NR	NR	NR	NR	NR	Just related pain	NR
Rana et al., 2014	NR	NR	NR	NR	NR	NR	NR	NR	Non-localized pain; Dystonic pain; Neuropathic pain; Akathesic pain; Constant
Paul et al., 2014	NR	NR	NR	NR	NR	NR	NR	NR	Ford Classification
Mao et al., 2015	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ohara et al., 2015	NR	NR	NR	NR	NR	NR	NR	Patients complaining of back pain were included in the study unless the etiologies of pain were not apparent.	NR
Priebe et al., 2015	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tekin., 2015	X	X	NR	NR	NR	NR	NR	Past lesions and pains that persisted ≥ two months were defined as chronic	NR

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Valkovic et al., 2015	NR	NR	NR	NR	NR	NR	NR	NR	Ford Classification
Allen et al., 2016	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gundogdu et al., 2016	X	X	NR	NR	NR	NR	NR	Ford Classification	NR
Kubo et al., 2016	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lin et al., 2016	NR	NR	NR	NR	X	NR	NR	NR	Neuropathic pain; Skeletal pain; neuralgia of the nerve root; dystonia pain; central pain; akathisia
Polli et al., 2016	NR	NR	NR	NR	X	NR	NR	In the PD-pain group, we included only patients who had persistent pain for more than 3 months and recurrent or daily pain (KPPS >2)	LANSS e KPPS
Rana et al., 2016[1]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rana et al., 2016[2]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rana et al., 2016[3]	NR	NR	NR	NR	NR	NR	NR	NR	BPI pain characteristics
Rodriguez-Violante et al., 2016	NR	NR	NR	NR	NR	NR	NR	NR	KPPS

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Buhmann et al., 2017	X	X	NR	NR	NR	NR	NR	NR	NR
Choi et al., 2017[1]	N	X	NR	NR	NR	NR	NR	Persistent pain > 3 months	Ford Classification
Choi et al, 2017[2]	N	X	NR	NR	NR	NR	NR	Persistent pain > 3 months	Ford Classification
Defazio et al., 2017	NR	NR	NR	NR	NR	NR	NR	NR	Ford Classification
Lien et al., 2017	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ozturk et al., 2017	N	X	NR	NR	NR	NR	NR	Persistent pain > 3 months	Ford Classification
Rana et al., 2017	NR	NR	NR	NR	NR	NR	NR	NR	NR
Adewusi et al., 2018	NR	NR	NR	NR	X	NR	NR	NR	Michigan N europatia Screening Instrument and KPPS
Fu et al., 2018	N	X	NR	NR	NR	NR	NR	Persistent pain > 3 months	Ford Classification
Galazky et al., 2018	X	X	NR	NR	NR	NR	NR	NR	NR
Ozturk & Kocer 2018	N	X	NR	NR	NR	NR	NR	Persistent pain > 3 months	NR
Rana et al., 2018[1]	NR	NR	NR	NR	NR	NR	NR	NR	BPI pain characteristics
Rana et al., 2018[2]	NR	NR	NR	NR	NR	NR	NR	NR	BPI pain characteristics
Rana et al., 2018[3]	NR	NR	NR	NR	NR	NR	NR	NR	BPI pain characteristics

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Scalzo et al., 2018	NR	NR	NR	NR	NR	NR	NR	NR	NR
Silva et al., 2018	NR	NR	NR	NR	NR	NR	NR	NR	NR
Silverdale et al., 2018	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Suzuki et al., 2018	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zella et al., 2018	NR	X	NR	NR	NR	NR	NR	Persistent pain > 12 weeks	NR
Alwardat et al., 2019[1]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alwardat et al., 2019[2]	NR	NR	NR	NR	NR	NR	NR	NR	NR
De Mattos et al., 2019	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Hirsi et al., 2019	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Joseph et al., 2019	NR	NR	NR	NR	NR	NR	NR	NR	NR
Martinez-Martin et al., 2019	NR	NR	NR	NR	NR	NR	NR	Declared unexplained pain in Item 10 of the NMSQ	KPPS
Rana et al., 2019	NR	NR	NR	NR	NR	NR	NR	NR	BPI pain characteristics
Vila-Chã et al., 2019[1]	NR	NR	NR	NR	NR	NR	NR	NR	Ford Classification
Vila- Chã et al., 2019[2]	NR	NR	NR	NR	NR	NR	NR	NR	Ford Classification

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Cruz-Almeida et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Faccio et al., 2020	X	X	NR	NR	NR	NR	NR	NR	NR
Florin et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Geroin et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ghosh et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Gonçalves et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kobylecki et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	KPPS e LANSS
Nguy, 2020	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Rocha- Filho & Souza-Lima, 2020	NR	NR	NR	NR	NR	NR	NR	NR	Headaches were classified according to the diagnostic criteria established by the third edition of the International Headache Classification (ICHD-3 beta)
Silveira Barezania et al., 2020	N	X	NR	NR	NR	NR	NR	Persistent pain > 3 months	NR
Sung et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR

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Walmsley et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yilmaz et al., 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Agrawal et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Kinugawa et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kurihara et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Liguori et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	KPPS
Lopes et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Naisby, et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
O'Neill et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	KPPS e LANSS
Paul et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Prell et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Vila-Chã et al., 2021	NR	NR	NR	NR	NR	NR	NR	NR	Ford Classification
Gao et al., 2022	NR	NR	NR	NR	NR	NR	NR	People with PD reporting pain	NR
Gültekin et al., 2022	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kinugawa et al., 2022	NR	NR	NR	NR	X	NR	NR	NR	NR

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Li et al., 2022	NR	NR	NR	NR	NR	NR	NR	NR	Ford Classification
Samanci co., 2022	NR	NR	NR	NR	NR	NR	NR	NR	Ford Classification
Sung & Kang, 2022	NR	NR	X	NR	NR	NR	NR	NR	Ford Classification

NR: Not Reported; X: You used the criterion.

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ANEXO

Ferramentas de Avaliação da Qualidade dos Estudos

Study Quality Assessment Tools

In 2013, NHLBI developed a set of tailored quality assessment tools to assist reviewers in focusing on concepts that are key to a study's internal validity. The tools were specific to certain study designs and tested for potential flaws in study methods or implementation. Experts used the tools during the systematic evidence review process to update existing clinical guidelines, such as those on cholesterol, blood pressure, and obesity. Their findings are outlined in the following reports:

- Assessing Cardiovascular Risk: Systematic Evidence Review from the Risk Assessment Work Group
- Management of Blood Cholesterol in Adults: Systematic Evidence Review from the Cholesterol Expert Panel
- Management of Blood Pressure in Adults: Systematic Evidence Review from the Blood Pressure Expert Panel
- Managing Overweight and Obesity in Adults: Systematic Evidence Review from the Obesity Expert Panel

While these tools have not been independently published and would not be considered standardized, they may be useful to the research community. These reports describe how experts used the tools for the project. Researchers may want to use the tools for their own projects; however, they would need to determine their own parameters for making judgements. Details about the design and application of the tools are included in Appendix A of the reports.

Quality Assessment of Controlled Intervention Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?			
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?			
3. Was the treatment allocation concealed (so that assignments could not be predicted)?			

Criteria	Yes	No	Other (CD, NR, NA)*
4. Were study participants and providers blinded to treatment group assignment?			
5. Were the people assessing the outcomes blinded to the participants' group assignments?			
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?			
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?			
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?			

Criteria	Yes	No	Other (CD, NR, NA)*
9. Was there high adherence to the intervention protocols for each treatment group?			
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?			
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?			
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?			

Criteria	Yes	No	Other (CD, NR, NA)*
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?			

Quality Rating (Good, Fair, or Poor)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for Assessing the Quality of Controlled Intervention Studies

The guidance document below is organized by question number from the tool for quality assessment of controlled intervention studies.

Question 1. Described as randomized

Was the study described as randomized? A study does not satisfy quality criteria as randomized simply because the authors call it randomized; however, it is a first step in determining if a study is randomized

Questions 2 and 3. Treatment allocation–two interrelated pieces

Adequate randomization: Randomization is adequate if it occurred according to the play of chance (e.g., computer generated sequence in more recent studies, or random number table in older studies).
Inadequate randomization: Randomization is inadequate if there is a preset plan (e.g., alternation where every other subject is assigned to treatment arm or another method of allocation is used, such as time or day of hospital admission or clinic visit, ZIP Code, phone number, etc.). In fact, this is not randomization at all–it is another method of assignment to groups. If assignment is not by the play of chance, then the answer to this question is no.
There may be some tricky scenarios that will need to be read carefully and considered for the role of chance in assignment. For example, randomization may occur at the site level, where all individuals at a particular site are assigned to receive treatment or no treatment. This scenario is used for group-randomized trials, which can be truly randomized, but often are "quasi-experimental" studies with comparison groups rather than true control groups. (Few, if any, group-randomized trials are anticipated for this evidence review.)

Allocation concealment: This means that one does not know in advance, or cannot guess accurately, to what group the next person eligible for randomization will be assigned. Methods include sequentially numbered opaque sealed envelopes, numbered or coded containers, central randomization by a coordinating center, computer-generated randomization that is not revealed ahead of time, etc.

Questions 4 and 5. Blinding

Blinding means that one does not know to which group–intervention or control–the participant is assigned. It is also sometimes called "masking." The reviewer assessed whether each of the following was blinded to knowledge of treatment assignment: (1) the person assessing the primary outcome(s) for the study (e.g., taking the measurements such as blood pressure, examining health records for events such as myocardial infarction, reviewing and interpreting test results such as x ray or cardiac catheterization findings); (2) the person receiving the intervention (e.g., the patient or other study participant); and (3) the person providing the intervention (e.g., the physician, nurse, pharmacist, dietitian, or behavioral interventionist).

Generally placebo-controlled medication studies are blinded to patient, provider, and outcome assessors; behavioral, lifestyle, and surgical studies are examples of studies that are frequently blinded only to the outcome assessors because blinding of the persons providing and receiving the interventions is difficult in these situations. Sometimes the individual providing the intervention is the same person performing the outcome assessment. This was noted when it occurred.

Question 6. Similarity of groups at baseline

This question relates to whether the intervention and control groups have similar baseline characteristics on average especially those characteristics that may affect the intervention or outcomes. The point of randomized trials is to create groups that are as similar as possible except for the intervention(s) being studied in order to compare the effects of the interventions between

groups. When reviewers abstracted baseline characteristics, they noted when there was a significant difference between groups. Baseline characteristics for intervention groups are usually presented in a table in the article (often Table 1).

Groups can differ at baseline without raising red flags if: (1) the differences would not be expected to have any bearing on the interventions and outcomes; or (2) the differences are not statistically significant. When concerned about baseline difference in groups, reviewers recorded them in the comments section and considered them in their overall determination of the study quality.

Questions 7 and 8. Dropout

"Dropouts" in a clinical trial are individuals for whom there are no end point measurements, often because they dropped out of the study and were lost to followup.

Generally, an acceptable overall dropout rate is considered 20 percent or less of participants who were randomized or allocated into each group. An acceptable differential dropout rate is an absolute difference between groups of 15 percentage points at most (calculated by subtracting the dropout rate of one group minus the dropout rate of the other group). However, these are general rates. Lower overall dropout rates are expected in shorter studies, whereas higher overall dropout rates may be acceptable for studies of longer duration. For example, a 6-month study of weight loss interventions should be expected to have nearly 100 percent followup (almost no dropouts–nearly everybody gets their weight measured regardless of whether or not they actually received the intervention), whereas a 10-year study testing the effects of intensive blood pressure lowering on heart attacks may be acceptable if there is a 20-25 percent dropout rate, especially if the dropout rate between groups was similar. The panels for the NHLBI systematic reviews may set different levels of dropout caps.

Conversely, differential dropout rates are not flexible; there should be a 15 percent cap. If there is a differential dropout rate of 15 percent or higher between arms, then there is a serious potential for

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Conversely, differential dropout rates are not flexible; there should be a 15 percent cap. If there is a differential dropout rate of 15 percent or higher between arms, then there is a serious potential for

https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools 8/58

bias. This constitutes a fatal flaw, resulting in a poor quality rating for the study.

Question 9. Adherence

Did participants in each treatment group adhere to the protocols for assigned interventions? For example, if Group 1 was assigned to 10 mg/day of Drug A, did most of them take 10 mg/day of Drug A? Another example is a study evaluating the difference between a 30-pound weight loss and a 10-pound weight loss on specific clinical outcomes (e.g., heart attacks), but the 30-pound weight loss group did not achieve its intended weight loss target (e.g., the group only lost 14 pounds on average). A third example is whether a large percentage of participants assigned to one group "crossed over" and got the intervention provided to the other group. A final example is when one group that was assigned to receive a particular drug at a particular dose had a large percentage of participants who did not end up taking the drug or the dose as designed in the protocol.

Question 10. Avoid other interventions

Changes that occur in the study outcomes being assessed should be attributable to the interventions being compared in the study. If study participants receive interventions that are not part of the study protocol and could affect the outcomes being assessed, and they receive these interventions differentially, then there is cause for concern because these interventions could bias results. The following scenario is another example of how bias can occur. In a study comparing two different dietary interventions on serum cholesterol, one group had a significantly higher percentage of participants taking statin drugs than the other group. In this situation, it would be impossible to know if a difference in outcome was due to the dietary intervention or the drugs.

Question 11. Outcome measures assessment

What tools or methods were used to measure the outcomes in the study? Were the tools and methods accurate and reliable–for example, have they been validated, or are they objective? This is important as it indicates the confidence you can have in the reported outcomes. Perhaps even more

important is ascertaining that outcomes were assessed in the same manner within and between groups. One example of differing methods is self-report of dietary salt intake versus urine testing for sodium content (a more reliable and valid assessment method). Another example is using BP measurements taken by practitioners who use their usual methods versus using BP measurements done by individuals trained in a standard approach. Such an approach may include using the same instrument each time and taking an individual's BP multiple times. In each of these cases, the answer to this assessment question would be "no" for the former scenario and "yes" for the latter. In addition, a study in which an intervention group was seen more frequently than the control group, enabling more opportunities to report clinical events, would not be considered reliable and valid.

Question 12. Power calculation

Generally, a study's methods section will address the sample size needed to detect differences in primary outcomes. The current standard is at least 80 percent power to detect a clinically relevant difference in an outcome using a two-sided alpha of 0.05. Often, however, older studies will not report on power.

Question 13. Prespecified outcomes

Investigators should prespecify outcomes reported in a study for hypothesis testing–which is the reason for conducting an RCT. Without prespecified outcomes, the study may be reporting ad hoc analyses, simply looking for differences supporting desired findings. Investigators also should prespecify subgroups being examined. Most RCTs conduct numerous post hoc analyses as a way of exploring findings and generating additional hypotheses. The intent of this question is to give more weight to reports that are not simply exploratory in nature.

Question 14. Intention-to-treat analysis

Intention-to-treat (ITT) means everybody who was randomized is analyzed according to the original group to which they are assigned. This is an extremely important concept because conducting an ITT

analysis preserves the whole reason for doing a randomized trial; that is, to compare groups that differ only in the intervention being tested. When the ITT philosophy is not followed, groups being compared may no longer be the same. In this situation, the study would likely be rated poor. However, if an investigator used another type of analysis that could be viewed as valid, this would be explained in the "other" box on the quality assessment form. Some researchers use a completers analysis (an analysis of only the participants who completed the intervention and the study), which introduces significant potential for bias. Characteristics of participants who do not complete the study are unlikely to be the same as those who do. The likely impact of participants withdrawing from a study treatment must be considered carefully. ITT analysis provides a more conservative (potentially less biased) estimate of effectiveness.

General Guidance for Determining the Overall Quality Rating of Controlled Intervention Studies

The questions on the assessment tool were designed to help reviewers focus on the key concepts for evaluating a study's internal validity. They are not intended to create a list that is simply tallied up to arrive at a summary judgment of quality.

Internal validity is the extent to which the results (effects) reported in a study can truly be attributed to the intervention being evaluated and not to flaws in the design or conduct of the study–in other words, the ability for the study to make causal conclusions about the effects of the intervention being tested. Such flaws can increase the risk of bias. Critical appraisal involves considering the risk of potential for allocation bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues addressed in the questions above. High risk of bias translates to a rating of poor quality. Low risk of bias translates to a rating of good quality.

Fatal flaws: If a study has a "fatal flaw," then risk of bias is significant, and the study is of poor quality. Examples of fatal flaws in RCTs include high dropout rates, high differential dropout rates, no ITT analysis or other unsuitable statistical analysis (e.g., completers-only analysis).

Generally, when evaluating a study, one will not see a "fatal flaw;" however, one will find some risk of bias. During training, reviewers were instructed to look for the potential for bias in studies by focusing on the concepts underlying the questions in the tool. For any box checked "no," reviewers were told to ask: "What is the potential risk of bias that may be introduced by this flaw?" That is, does this factor cause one to doubt the results that were reported in the study?

NHLBI staff provided reviewers with background reading on critical appraisal, while emphasizing that the best approach to use is to think about the questions in the tool in determining the potential for bias in a study. The staff also emphasized that each study has specific nuances; therefore, reviewers should familiarize themselves with the key concepts.

Quality Assessment of Systematic Reviews and Meta-Analyses

Criteria	Yes	No	Other (CD, NR, NA)*

Criteria	Yes	No	Other (CD, NR, NA)*
1. Is the review based on a focused question that is adequately formulated and described?			
2. Were eligibility criteria for included and excluded studies predefined and specified?			
3. Did the literature search strategy use a comprehensive, systematic approach?			
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?			

Criteria	Yes	No	Other (CD, NR, NA)*
5. Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?			
6. Were the included studies listed along with important characteristics and results of each study?			
7. Was publication bias assessed?			
8. Was heterogeneity assessed? (This question applies only to meta-analyses.)			

Quality Rating (Good, Fair, or Poor)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for Quality Assessment Tool for Systematic Reviews and Meta-Analyses

A systematic review is a study that attempts to answer a question by synthesizing the results of primary studies while using strategies to limit bias and random error.424 These strategies include a comprehensive search of all potentially relevant articles and the use of explicit, reproducible criteria in the selection of articles included in the review. Research designs and study characteristics are appraised, data are synthesized, and results are interpreted using a predefined systematic approach that adheres to evidence-based methodological principles.

Systematic reviews can be qualitative or quantitative. A qualitative systematic review summarizes the results of the primary studies but does not combine the results statistically. A quantitative systematic review, or meta-analysis, is a type of systematic review that employs statistical techniques to

combine the results of the different studies into a single pooled estimate of effect, often given as an odds ratio. The guidance document below is organized by question number from the tool for quality assessment of systematic reviews and meta-analyses.

Question 1. Focused question

The review should be based on a question that is clearly stated and well-formulated. An example would be a question that uses the PICO (population, intervention, comparator, outcome) format, with all components clearly described.

Question 2. Eligibility criteria

The eligibility criteria used to determine whether studies were included or excluded should be clearly specified and predefined. It should be clear to the reader why studies were included or excluded.

Question 3. Literature search

The search strategy should employ a comprehensive, systematic approach in order to capture all of the evidence possible that pertains to the question of interest. At a minimum, a comprehensive review has the following attributes:

- Electronic searches were conducted using multiple scientific literature databases, such as MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, PsychLit, and others as appropriate for the subject matter.
- Manual searches of references found in articles and textbooks should supplement the electronic searches.

Additional search strategies that may be used to improve the yield include the following:

- Studies published in other countries

- Studies published in languages other than English
- Identification by experts in the field of studies and articles that may have been missed
- Search of grey literature, including technical reports and other papers from government agencies or scientific groups or committees; presentations and posters from scientific meetings, conference proceedings, unpublished manuscripts; and others. Searching the grey literature is important (whenever feasible) because sometimes only positive studies with significant findings are published in the peer-reviewed literature, which can bias the results of a review.

In their reviews, researchers described the literature search strategy clearly, and ascertained it could be reproducible by others with similar results.

Question 4. Dual review for determining which studies to include and exclude

Titles, abstracts, and full-text articles (when indicated) should be reviewed by two independent reviewers to determine which studies to include and exclude in the review. Reviewers resolved disagreements through discussion and consensus or with third parties. They clearly stated the review process, including methods for settling disagreements.

Question 5. Quality appraisal for internal validity

Each included study should be appraised for internal validity (study quality assessment) using a standardized approach for rating the quality of the individual studies. Ideally, this should be done by at least two independent reviewers appraised each study for internal validity. However, there is not one commonly accepted, standardized tool for rating the quality of studies. So, in the research papers, reviewers looked for an assessment of the quality of each study and a clear description of the process used.

Question 6. List and describe included studies

All included studies were listed in the review, along with descriptions of their key characteristics. This was presented either in narrative or table format.

Question 7. Publication bias

Publication bias is a term used when studies with positive results have a higher likelihood of being published, being published rapidly, being published in higher impact journals, being published in English, being published more than once, or being cited by others.425,426 Publication bias can be linked to favorable or unfavorable treatment of research findings due to investigators, editors, industry, commercial interests, or peer reviewers. To minimize the potential for publication bias, researchers can conduct a comprehensive literature search that includes the strategies discussed in Question 3.

A funnel plot–a scatter plot of component studies in a meta-analysis–is a commonly used graphical method for detecting publication bias. If there is no significant publication bias, the graph looks like a symmetrical inverted funnel.

Reviewers assessed and clearly described the likelihood of publication bias.

Question 8. Heterogeneity

Heterogeneity is used to describe important differences in studies included in a meta-analysis that may make it inappropriate to combine the studies.427 Heterogeneity can be clinical (e.g., important differences between study participants, baseline disease severity, and interventions); methodological (e.g., important differences in the design and conduct of the study); or statistical (e.g., important differences in the quantitative results or reported effects).

Researchers usually assess clinical or methodological heterogeneity qualitatively by determining whether it makes sense to combine studies. For example:

- Should a study evaluating the effects of an intervention on CVD risk that involves elderly male smokers with hypertension be combined with a study that involves healthy adults ages 18 to 40? (Clinical Heterogeneity)
- Should a study that uses a randomized controlled trial (RCT) design be combined with a study that uses a case-control study design? (Methodological Heterogeneity)

Statistical heterogeneity describes the degree of variation in the effect estimates from a set of studies; it is assessed quantitatively. The two most common methods used to assess statistical heterogeneity are the Q test (also known as the X2 or chi-square test) or I2 test.

Reviewers examined studies to determine if an assessment for heterogeneity was conducted and clearly described. If the studies are found to be heterogeneous, the investigators should explore and explain the causes of the heterogeneity, and determine what influence, if any, the study differences had on overall study results.

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*

Criteria	Yes	No	Other (CD, NR, NA)*
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%?			
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?			

Criteria	Yes	No	Other (CD, NR, NA)*
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?			

Criteria	Yes	No	Other (CD, NR, NA)*
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)?			

Quality Rating (Good, Fair, or Poor)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for Assessing the Quality of Observational Cohort and Cross-Sectional Studies

The guidance document below is organized by question number from the tool for quality assessment of observational cohort and cross-sectional studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality

scientific research explicitly defines a research question.

Questions 2 and 3. Study population

Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interest at the time they were recruited?

An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994. In this example, the population is clearly described as: (1) who (men over 40 years old with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women ages 34 to 59 years of age in 1980 who were in the nursing profession and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards.

In cohort studies, it is crucial that the population at baseline is free of the outcome of interest. For example, the nurses' population above would be an appropriate group in which to study incident coronary disease. This information is usually found either in descriptions of population recruitment, definitions of variables, or inclusion/exclusion criteria.

You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list.

If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.

Question 4. Groups recruited from the same population and uniform eligibility criteria

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

Most cohort studies begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies–which is when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for cardiovascular disease than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic. This study recruits groups from different clinic populations, so this example would get a "no."

However, the women nurses described in the question above were selected based on the same inclusion/exclusion criteria, so that example would get a "yes."

Question 5. Sample size justification

Did the authors present their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed.

A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates

of effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes."

However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question–i.e., it may have been an exploratory, hypothesis-generating study.

Question 6. Exposure assessed prior to outcome measurement

This question is important because, in order to determine whether an exposure causes an outcome, the exposure must come before the outcome.

For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort (large epidemiological studies like Framingham used this approach). However, for other cohort studies, the cohort is selected based on its exposure status, as in the example above of depressed diabetic men (the exposure being depression). Other examples include a cohort identified by its exposure to fluoridated drinking water and then compared to a cohort living in an area without fluoridated water, or a cohort of military personnel exposed to combat in the Gulf War compared to a cohort of military personnel not deployed in a combat zone.

With either of these types of cohort studies, the cohort is followed forward in time (i.e., prospectively) to assess the outcomes that occurred in the exposed members compared to nonexposed members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly,

the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred.

For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and nonexposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome.

Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data), where the exposures and outcomes are measured during the same timeframe. As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Question 6 should be "no."

Question 7. Sufficient timeframe to see an effect

Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? In the examples given above, if clinical depression has a biological effect on increasing risk for CVD, such an effect may take years. In the other example, if higher dietary sodium increases BP, a short timeframe may be sufficient to assess its association with BP, but a longer timeframe would be needed to examine its association with heart attacks.

The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined.

Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.

Question 8. Different levels of the exposure of interest

If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed? (for example, for drugs: not on the medication, on a low dose, medium dose, high dose; for dietary sodium, higher than average U.S. consumption, lower than recommended consumption, between the two). Sometimes discrete categories of exposure are not used, but instead exposures are measured as continuous variables (for example, mg/day of dietary sodium or BP values).

In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose-response relationships between exposures and outcomes–e.g., the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose-response relationships lends credibility to the hypothesis of causality between exposure and outcome.

For some exposures, however, this question may not be applicable (e.g., the exposure may be a dichotomous variable like living in a rural setting versus an urban setting, or vaccinated/not vaccinated with a one-time vaccine). If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively towards the quality rating.

Question 9. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable–for example, have they been validated or are they objective? This issue is important as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP, where there may be quite a difference between usual care, where clinicians measure BP however it is done in their practice setting (which can vary considerably), and use of trained BP assessors using standardized equipment (e.g., the same BP device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged). In each of these cases, the former would get a "no" and the latter a "yes."

Here is a final example that illustrates the point about why it is important to assess exposures consistently across all groups: If people with higher BP (exposed cohort) are seen by their providers more frequently than those without elevated BP (nonexposed group), it also increases the chances of detecting and documenting changes in health outcomes, including CVD-related events. Therefore, it may lead to the conclusion that higher BP leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher BP were seen more often; thus, more CVD-related events were detected and documented simply because they had more encounters with the health care system. Thus, it could bias the results and lead to an erroneous conclusion.

Question 10. Repeated exposure assessment

Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified. Also, multiple measurements enable investigators to look at changes in exposure over time, for example, people who ate high dietary sodium throughout the followup period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

Question 11. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable–for example, have they been validated or are they objective? This issue is important because it influences confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups.

An example of an outcome measure that is objective, accurate, and reliable is death–the outcome measured with more accuracy than any other. But even with a measure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (if body weight is the outcome of interest).

Similar to the example in Question 9, results may be biased if one group (e.g., people with high BP) is seen more frequently than another group (people with normal BP) because more frequent encounters with the health care system increases the chances of outcomes being detected and documented.

Question 12. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same

person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not involved in the care of the patient and had no information about the study participants' exposure status. The committee would then be provided with copies of participants' medical records, which had been stripped of any potential exposure information or personally identifiable information. The committee would then review the records for prespecified outcomes according to the study protocol. If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 13. Followup rate

Higher overall followup rates are always better than lower followup rates, even though higher rates are expected in shorter studies, whereas lower overall followup rates are often seen in studies of longer duration. Usually, an acceptable overall followup rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90 percent followup, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent followup rate.

Question 14. Statistical analyses

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome–that are not of interest to the research question–should be controlled for in the analyses.

For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

Some general guidance for determining the overall quality rating of observational cohort and cross-sectional studies

The questions on the form are designed to help you focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for cohort studies is the extent to which the results reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study–in other words, the ability of the study to draw associative conclusions about the effects of the exposures being studied on outcomes. Any such flaws can increase the risk of bias.

Critical appraisal involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of poor quality. Low risk of bias translates to a rating of good quality. (Thus, the greater the risk of bias, the lower the quality rating of the study.)

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the exposure and outcome, the higher quality the study. These include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding–all concepts reflected in the tool.

Generally, when you evaluate a study, you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no" you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the study or doubt the ability of the study to accurately assess an association between exposure and outcome?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and consideration of the concepts for minimizing bias.

Quality Assessment of Case-Control Studies

Criteria	Yes	No	Other (CD, NR, NA)*
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 (**Good, Fair, or Poor**) (see guidance)
Rater #1 Initials:
Rater #2 Initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for Assessing the Quality of Case-Control Studies

The guidance document below is organized by question number from the tool for quality assessment of case-control studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. High quality scientific research explicitly defines a research question.

Question 2. Study population

Did the authors describe the group of individuals from which the cases and controls were selected or recruited, while using demographics, location, and time period? If the investigators conducted this study again, would they know exactly who to recruit, from where, and from what time period?

Investigators identify case-control study populations by location, time period, and inclusion criteria for cases (individuals with the disease, condition, or problem) and controls (individuals without the disease, condition, or problem). For example, the population for a study of lung cancer and chemical exposure would be all incident cases of lung cancer diagnosed in patients ages 35 to 79, from January 1, 2003 to December 31, 2008, living in Texas during that entire time period, as well as controls without lung cancer recruited from the same population during the same time period. The population is clearly described as: (1) who (men and women ages 35 to 79 with (cases) and without (controls) incident lung cancer); (2) where (living in Texas); and (3) when (between January 1, 2003 and December 31, 2008).

Other studies may use disease registries or data from cohort studies to identify cases. In these cases, the populations are individuals who live in the area covered by the disease registry or included in a cohort study (i.e., nested case-control or case-cohort). For example, a study of the relationship between vitamin D intake and myocardial infarction might use patients identified via the GRACE registry, a database of heart attack patients.

NHLBI staff encouraged reviewers to examine prior papers on methods (listed in the reference list) to make this assessment, if necessary.

Question 3. Target population and case representation

In order for a study to truly address the research question, the target population–the population from which the study population is drawn and to which study results are believed to apply–should be carefully defined. Some authors may compare characteristics of the study cases to characteristics of cases in the target population, either in text or in a table. When study cases are shown to be representative of cases in the appropriate target population, it increases the likelihood that the study was well-designed per the research question.

However, because these statistics are frequently difficult or impossible to measure, publications should not be penalized if case representation is not shown. For most papers, the response to question 3 will be "NR." Those subquestions are combined because the answer to the second subquestion–case representation–determines the response to this item. However, it cannot be determined without considering the response to the first subquestion. For example, if the answer to the first subquestion is "yes," and the second, "CD," then the response for item 3 is "CD."

Question 4. Sample size justification

Did the authors discuss their reasons for selecting or recruiting the number of individuals included? Did they discuss the statistical power of the study and provide a sample size calculation to ensure that the study is adequately powered to detect an association (if one exists)? This question does not refer to a description of the manner in which different groups were included or excluded using the inclusion/exclusion criteria (e.g., "Final study size was 1,378 participants after exclusion of 461 patients with missing data" is not considered a sample size justification for the purposes of this question).

An article's methods section usually contains information on sample size and the size needed to detect differences in exposures and on statistical power.

Question 5. Groups recruited from the same population

To determine whether cases and controls were recruited from the same population, one can ask hypothetically, "If a control was to develop the outcome of interest (the condition that was used to select cases), would that person have been eligible to become a case?" Case-control studies begin with the selection of the cases (those with the outcome of interest, e.g., lung cancer) and controls (those in whom the outcome is absent). Cases and controls are then evaluated and categorized by their exposure status. For the lung cancer example, cases and controls were recruited from hospitals in a given region. One may reasonably assume that controls in the catchment area for the hospitals, or those already in the hospitals for a different reason, would attend those hospitals if they became a case; therefore, the controls are drawn from the same population as the cases. If the controls were recruited or selected from a different region (e.g., a State other than Texas) or time period (e.g., 1991-2000), then the cases and controls were recruited from different populations, and the answer to this question would be "no."

The following example further explores selection of controls. In a study, eligible cases were men and women, ages 18 to 39, who were diagnosed with atherosclerosis at hospitals in Perth, Australia, between July 1, 2000 and December 31, 2007. Appropriate controls for these cases might be sampled using voter registration information for men and women ages 18 to 39, living in Perth (population-based controls); they also could be sampled from patients without atherosclerosis at the same hospitals (hospital-based controls). As long as the controls are individuals who would have been eligible to be included in the study as cases (if they had been diagnosed with atherosclerosis), then the controls were selected appropriately from the same source population as cases.

In a prospective case-control study, investigators may enroll individuals as cases at the time they are found to have the outcome of interest; the number of cases usually increases as time progresses. At this same time, they may recruit or select controls from the population without the outcome of interest. One way to identify or recruit cases is through a surveillance system. In turn, investigators can select controls from the population covered by that system. This is an example of population-based controls. Investigators also may identify and select cases from a cohort study population and

identify controls from outcome-free individuals in the same cohort study. This is known as a nested case-control study.

Question 6. Inclusion and exclusion criteria prespecified and applied uniformly

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the groups involved? To answer this question, reviewers determined if the investigators developed I/E criteria prior to recruitment or selection of the study population and if they used the same underlying criteria for all groups. The investigators should have used the same selection criteria, except for study participants who had the disease or condition, which would be different for cases and controls by definition. Therefore, the investigators use the same age (or age range), gender, race, and other characteristics to select cases and controls. Information on this topic is usually found in a paper's section on the description of the study population.

Question 7. Case and control definitions

For this question, reviewers looked for descriptions of the validity of case and control definitions and processes or tools used to identify study participants as such. Was a specific description of "case" and "control" provided? Is there a discussion of the validity of the case and control definitions and the processes or tools used to identify study participants as such? They determined if the tools or methods were accurate, reliable, and objective. For example, cases might be identified as "adult patients admitted to a VA hospital from January 1, 2000 to December 31, 2009, with an ICD-9 discharge diagnosis code of acute myocardial infarction and at least one of the two confirmatory findings in their medical records: at least 2mm of ST elevation changes in two or more ECG leads and an elevated troponin level. Investigators might also use ICD-9 or CPT codes to identify patients. All cases should be identified using the same methods. Unless the distinction between cases and controls is accurate and reliable, investigators cannot use study results to draw valid conclusions.

Question 8. Random selection of study participants

If a case-control study did not use 100 percent of eligible cases and/or controls (e.g., not all disease-free participants were included as controls), did the authors indicate that random sampling was used to select controls? When it is possible to identify the source population fairly explicitly (e.g., in a nested case-control study, or in a registry-based study), then random sampling of controls is preferred. When investigators used consecutive sampling, which is frequently done for cases in prospective studies, then study participants are not considered randomly selected. In this case, the reviewers would answer "no" to Question 8. However, this would not be considered a fatal flaw.

If investigators included all eligible cases and controls as study participants, then reviewers marked "NA" in the tool. If 100 percent of cases were included (e.g., NA for cases) but only 50 percent of eligible controls, then the response would be "yes" if the controls were randomly selected, and "no" if they were not. If this cannot be determined, the appropriate response is "CD."

Question 9. Concurrent controls

A concurrent control is a control selected at the time another person became a case, usually on the same day. This means that one or more controls are recruited or selected from the population without the outcome of interest at the time a case is diagnosed. Investigators can use this method in both prospective case-control studies and retrospective case-control studies. For example, in a retrospective study of adenocarcinoma of the colon using data from hospital records, if hospital records indicate that Person A was diagnosed with adenocarcinoma of the colon on June 22, 2002, then investigators would select one or more controls from the population of patients without adenocarcinoma of the colon on that same day. This assumes they conducted the study retrospectively, using data from hospital records. The investigators could have also conducted this study using patient records from a cohort study, in which case it would be a nested case-control study.

Investigators can use concurrent controls in the presence or absence of matching and vice versa. A study that uses matching does not necessarily mean that concurrent controls were used.

Question 10. Exposure assessed prior to outcome measurement

Investigators first determine case or control status (based on presence or absence of outcome of interest), and then assess exposure history of the case or control; therefore, reviewers ascertained that the exposure preceded the outcome. For example, if the investigators used tissue samples to determine exposure, did they collect them from patients prior to their diagnosis? If hospital records were used, did investigators verify that the date a patient was exposed (e.g., received medication for atherosclerosis) occurred prior to the date they became a case (e.g., was diagnosed with type 2 diabetes)? For an association between an exposure and an outcome to be considered causal, the exposure must have occurred prior to the outcome.

Question 11. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable–for example, have they been validated or are they objective? This is important, as it influences confidence in the reported exposures. Equally important is whether the exposures were assessed in the same manner within groups and between groups. This question pertains to bias resulting from exposure misclassification (i.e., exposure ascertainment).

For example, a retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content because participants' retrospective recall of dietary salt intake may be inaccurate and result in misclassification of exposure status. Similarly, BP results from practices that use an established protocol for measuring BP would be considered more valid and reliable than results from practices that did not use standard protocols. A protocol may include using trained BP assessors, standardized equipment (e.g., the same BP device which has been tested and calibrated), and a standardized

procedure (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged).

Question 12. Blinding of exposure assessors

Blinding or masking means that outcome assessors did not know whether participants were exposed or unexposed. To answer this question, reviewers examined articles for evidence that the outcome assessor(s) was masked to the exposure status of the research participants. An outcome assessor, for example, may examine medical records to determine the outcomes that occurred in the exposed and comparison groups. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status. A reviewer would note such a finding in the comments section of the assessment tool.

One way to ensure good blinding of exposure assessment is to have a separate committee, whose members have no information about the study participants' status as cases or controls, review research participants' records. To help answer the question above, reviewers determined if it was likely that the outcome assessor knew whether the study participant was a case or control. If it was unlikely, then the reviewers marked "no" to Question 12. Outcome assessors who used medical records to assess exposure should not have been directly involved in the study participants' care, since they probably would have known about their patients' conditions. If the medical records contained information on the patient's condition that identified him/her as a case (which is likely), that information would have had to be removed before the exposure assessors reviewed the records.

If blinding was not possible, which sometimes happens, the reviewers marked "NA" in the assessment tool and explained the potential for bias.

Question 13. Statistical analysis

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Investigators often use logistic regression or other regression methods to account for the influence of variables not of interest.

This is a key issue in case-controlled studies; statistical analyses need to control for potential confounders, in contrast to RCTs in which the randomization process controls for potential confounders. In the analysis, investigators need to control for all key factors that may be associated with both the exposure of interest and the outcome and are not of interest to the research question.

A study of the relationship between smoking and CVD events illustrates this point. Such a study needs to control for age, gender, and body weight; all are associated with smoking and CVD events. Well-done case-control studies control for multiple potential confounders.

Matching is a technique used to improve study efficiency and control for known confounders. For example, in the study of smoking and CVD events, an investigator might identify cases that have had a heart attack or stroke and then select controls of similar age, gender, and body weight to the cases. For case-control studies, it is important that if matching was performed during the selection or recruitment process, the variables used as matching criteria (e.g., age, gender, race) should be controlled for in the analysis.

General Guidance for Determining the Overall Quality Rating of Case-Controlled Studies

NHLBI designed the questions in the assessment tool to help reviewers focus on the key concepts for evaluating a study's internal validity, not to use as a list from which to add up items to judge a study's quality.

Internal validity for case-control studies is the extent to which the associations between disease and exposure reported in the study can truly be attributed to the exposure being evaluated rather than to flaws in the design or conduct of the study. In other words, what is ability of the study to draw

associative conclusions about the effects of the exposures on outcomes? Any such flaws can increase the risk of bias.

In critical appraising a study, the following factors need to be considered: risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues addressed in the questions above. High risk of bias translates to a poor quality rating; low risk of bias translates to a good quality rating. Again, the greater the risk of bias, the lower the quality rating of the study.

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the outcome and the exposure, the higher the quality of the study. These include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding–all concepts reflected in the tool.

If a study has a "fatal flaw," then risk of bias is significant; therefore, the study is deemed to be of poor quality. An example of a fatal flaw in case-control studies is a lack of a consistent standard process used to identify cases and controls.

Generally, when reviewers evaluated a study, they did not see a "fatal flaw," but instead found some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, reviewers examined the potential for bias in the study. For any box checked "no," reviewers asked, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, did this factor lead to doubt about the results reported in the study or the ability of the study to accurately assess an association between exposure and outcome?

By examining questions in the assessment tool, reviewers were best able to assess the potential for bias in a study. Specific rules were not useful, as each study had specific nuances. In addition, being

familiar with the key concepts helped reviewers assess the studies. Examples of studies rated good, fair, and poor were useful, yet each study had to be assessed on its own.

Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?			
2. Were eligibility/selection criteria for the study population prespecified and clearly described?			
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			

Criteria	Yes	No	Other (CD, NR, NA)*
4. Were all eligible participants that met the prespecified entry criteria enrolled?			
5. Was the sample size sufficiently large to provide confidence in the findings?			
6. Was the test/service/intervention clearly described and delivered consistently across the study population?			
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?			
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?			

Criteria	Yes	No	Other (CD, NR, NA)*
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?			
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?			
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			

Quality Rating (**Good, Fair, or Poor**) (see guidance)
Rater #1 Initials:
Rater #2 Initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for Assessing the Quality of Before-After (Pre-Post) Studies With No Control Group

The guidance document below is organized by question number from the tool for quality assessment of controlled intervention studies.

Question 1. Study question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality

scientific research explicitly defines a research question.

Question 2. Eligibility criteria and study population

Did the authors describe the eligibility criteria applied to the individuals from whom the study participants were selected or recruited? In other words, if the investigators were to conduct this study again, would they know whom to recruit, from where, and from what time period?

Here is a sample description of a study population: men over age 40 with type 2 diabetes, who began seeking medical care at Phoenix Good Samaritan Hospital, between January 1, 2005 and December 31, 2007. The population is clearly described as: (1) who (men over age 40 with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 2005 and December 31, 2007). Another sample description is women who were in the nursing profession, who were ages 34 to 59 in 1995, had no known CHD, stroke, cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards.

To assess this question, reviewers examined prior papers on study methods (listed in reference list) when necessary.

Question 3. Study participants representative of clinical populations of interest

The participants in the study should be generally representative of the population in which the intervention will be broadly applied. Studies on small demographic subgroups may raise concerns about how the intervention will affect broader populations of interest. For example, interventions that focus on very young or very old individuals may affect middle-aged adults differently. Similarly, researchers may not be able to extrapolate study results from patients with severe chronic diseases to healthy populations.

Question 4. All eligible participants enrolled

To further explore this question, reviewers may need to ask: Did the investigators develop the I/E criteria prior to recruiting or selecting study participants? Were the same underlying I/E criteria used for all research participants? Were all subjects who met the I/E criteria enrolled in the study?

Question 5. Sample size

Did the authors present their reasons for selecting or recruiting the number of individuals included or analyzed? Did they note or discuss the statistical power of the study? This question addresses whether there was a sufficient sample size to detect an association, if one did exist.

An article's methods section may provide information on the sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power (such as, the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample size calculations. In any case, if the reviewers determined that the power was sufficient to detect the effects of interest, then they would answer "yes" to Question 5.

Question 6. Intervention clearly described

Another pertinent question regarding interventions is: Was the intervention clearly defined in detail in the study? Did the authors indicate that the intervention was consistently applied to the subjects? Did the research participants have a high level of adherence to the requirements of the intervention? For example, if the investigators assigned a group to 10 mg/day of Drug A, did most participants in this group take the specific dosage of Drug A? Or did a large percentage of participants end up not taking the specific dose of Drug A indicated in the study protocol?

Reviewers ascertained that changes in study outcomes could be attributed to study interventions. If participants received interventions that were not part of the study protocol and could affect the outcomes being assessed, the results could be biased.

Question 7. Outcome measures clearly described, valid, and reliable

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable–for example, have they been validated or are they objective? This question is important because the answer influences confidence in the validity of study results.

An example of an outcome measure that is objective, accurate, and reliable is death–the outcome measured with more accuracy than any other. But even with a measure as objective as death, differences can exist in the accuracy and reliability of how investigators assessed death. For example, did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example of a valid study is one whose objective is to determine if dietary fat intake affects blood cholesterol level (cholesterol level being the outcome) and in which the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes."

An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weight (if body weight is the outcome of interest).

Question 8. Blinding of outcome assessors

Blinding or masking means that the outcome assessors did not know whether the participants received the intervention or were exposed to the factor under study. To answer the question above, the reviewers examined articles for evidence that the person(s) assessing the outcome(s) was masked to the participants' intervention or exposure status. An outcome assessor, for example, may examine medical records to determine the outcomes that occurred in the exposed and comparison groups. Sometimes the person applying the intervention or measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would not likely be blinded to the intervention or exposure status. A reviewer would note such a finding in the comments section of the assessment tool.

In assessing this criterion, the reviewers determined whether it was likely that the person(s) conducting the outcome assessment knew the exposure status of the study participants. If not, then blinding was adequate. An example of adequate blinding of the outcome assessors is to create a separate committee whose members were not involved in the care of the patient and had no information about the study participants' exposure status. Using a study protocol, committee members would review copies of participants' medical records, which would be stripped of any potential exposure information or personally identifiable information, for prespecified outcomes.

Question 9. Followup rate

Higher overall followup rates are always desirable to lower followup rates, although higher rates are expected in shorter studies, and lower overall followup rates are often seen in longer studies. Usually an acceptable overall followup rate is considered 80 percent or more of participants whose interventions or exposures were measured at baseline. However, this is a general guideline.

In accounting for those lost to followup, in the analysis, investigators may have imputed values of the outcome for those lost to followup or used other methods. For example, they may carry forward the baseline value or the last observed value of the outcome measure and use these as imputed values for the final outcome measure for research participants lost to followup.

Question 10. Statistical analysis

Were formal statistical tests used to assess the significance of the changes in the outcome measures between the before and after time periods? The reported study results should present values for statistical tests, such as p values, to document the statistical significance (or lack thereof) for the changes in the outcome measures found in the study.

Question 11. Multiple outcome measures

Were the outcome measures for each person measured more than once during the course of the before and after study periods? Multiple measurements with the same result increase confidence that the outcomes were accurately measured.

Question 12. Group-level interventions and individual-level outcome efforts

Group-level interventions are usually not relevant for clinical interventions such as bariatric surgery, in which the interventions are applied at the individual patient level. In those cases, the questions were coded as "NA" in the assessment tool.

General Guidance for Determining the Overall Quality Rating of Before-After Studies

The questions in the quality assessment tool were designed to help reviewers focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list from which to add up items to judge a study's quality.

Internal validity is the extent to which the outcome results reported in the study can truly be attributed to the intervention or exposure being evaluated, and not to biases, measurement errors, or other confounding factors that may result from flaws in the design or conduct of the study. In other words, what is the ability of the study to draw associative conclusions about the effects of the interventions or exposures on outcomes?

Critical appraisal of a study involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of poor quality; low risk of bias translates to a rating of good quality. Again, the greater the risk of bias, the lower the quality rating of the study.

In addition, the more attention in the study design to issues that can help determine if there is a causal relationship between the exposure and outcome, the higher quality the study. These issues include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, and sufficient timeframe to see an effect.

Generally, when reviewers evaluate a study, they will not see a "fatal flaw," but instead will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, reviewers should ask themselves about the potential for bias in the study they are critically appraising. For any box checked "no" reviewers should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor lead to doubt about the results reported in the study or doubt about the ability of the study to accurately assess an association between the intervention or exposure and the outcome?

The best approach is to think about the questions in the assessment tool and how each one reveals something about the potential for bias in a study. Specific rules are not useful, as each study has specific nuances. In addition, being familiar with the key concepts will help reviewers be more comfortable with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own.

Quality Assessment Tool for Case Series Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?			
2. Was the study population clearly and fully described, including a case definition?			
3. Were the cases consecutive?			
4. Were the subjects comparable?			
5. Was the intervention clearly described?			
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?			

7. Was the length of follow-up adequate?			
8. Were the statistical methods well-described?			
9. Were the results well-described?			

Quality Rating (Good, Fair, or Poor)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Background: Development and Use

Learn more about the development and use of Study Quality Assessment Tools.

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