# Postprint: A Systematic Review of Factors Influencing Pain in Patients with Parkinson' s Disease

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## Abstract

Background: Pain is one of the common non-motor symptoms in patients with Parkinson' s disease (PD) and severely impacts their quality of life. Researchers have explored the influencing factors of pain in PD patients, but the findings have demonstrated inconsistencies.

Objective: To conduct a systematic evaluation of the influencing factors of pain in PD patients.

Methods: A computerized search was conducted across CNKI, Wanfang, VIP, China Biology Medicine disc (CBM), Web of Science, PubMed, MEDLINE, EmBase, and The Cochrane Library for studies on influencing factors of pain in PD patients, with the search period spanning from database inception to April 2022. Two researchers independently screened the literature and extracted relevant data. The Agency for Healthcare Research and Quality (AHRQ) scale and the Newcastle-Ottawa Scale (NOS) were employed to assess the risk of bias in cross-sectional studies and case-control studies, respectively. A descriptive analysis was performed on all involved influencing factors, and RevMan 5.3 software was utilized for meta-analysis of common influencing factors.

Results: A total of 16 studies were included, with an overall sample size of 2,855 cases, involving 24 types of influencing factors. The descriptive analysis revealed 2 protective factors and 22 risk factors. The meta-analysis results indicated that gender [OR=3.73, 95%CI (1.75, 7.96), P=0.0007], disease duration [OR=1.35, 95%CI (1.15, 1.60), P=0.0003], depressive mood [OR=1.14, 95%CI (1.07, 1.22), P<0.0001], UPDRS III score [OR=1.07, 95%CI (1.03, 1.11), P=0.0002], Hoehn-Yahr stage [OR=2.28, 95%CI (1.28, 4.04), P=0.005], and NMSS score [OR=1.68, 95%CI (1.46, 1.93), P<0.00001] were influencing factors of PD pain. GRADE analysis demonstrated that gender and NMSS score were of moderate-quality evidence, disease duration, depressive mood, and UPDRS III score were of low-quality evidence, and Hoehn-Yahr stage was of very low-quality evidence.

Conclusion: Normal cognitive function and good mental status are protective factors for PD pain, while female gender, long disease duration, depressive mood, motor disorders, high Hoehn-Yahr stage, and severe degree of other non-motor symptoms (sleep disorders, fatigue) are risk factors for PD pain. Future large-sample, high-quality studies are needed for further validation.

## Full Text

## Preamble

### Systematic Review of Factors Influencing Pain in Parkinson's Disease Patients

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## Abstract

**Background:** Pain is one of the common non-motor symptoms in Parkinson' s disease (PD) patients and seriously impacts their quality of life. Although scholars have explored the factors influencing pain occurrence in PD patients, research findings show considerable variation.

**Objective:** To systematically evaluate the factors influencing pain in PD patients.

**Methods:** Studies on factors influencing pain in PD patients were searched in CNKI, Wanfang, VIP, CBM, Web of Science, PubMed, MEDLINE, Embase, and The Cochrane Library from inception to April 2022. Two researchers independently screened literature and extracted relevant data. The risk of bias was assessed using the Agency for Healthcare Research and Quality (AHRQ)

scale for cross-sectional studies and the Newcastle-Ottawa Scale (NOS) for case-control studies. Descriptive analysis was conducted on all influencing factors, and meta-analysis of common factors was performed using RevMan 5.3 software.

**Results:** Sixteen studies with a total sample size of 2,855 cases involving 24 influencing factors were included. Descriptive analysis identified 2 protective factors and 22 risk factors. Meta-analysis revealed that gender [OR=3.73, 95%CI (1.75,7.96), P=0.0007], disease duration [OR=1.35, 95%CI (1.15,1.60), P=0.0003], depressive mood [OR=1.14, 95%CI (1.07,1.22), P<0.0001], UPDRS score [OR=1.07, 95%CI (1.03,1.11), P=0.0002], Hoehn-Yahr staging [OR=2.28, 95%CI (1.28,4.04), P=0.005], and NMSS score [OR=1.68, 95%CI (1.46,1.93), P<0.00001] were influencing factors for PD pain. GRADE analysis indicated moderate-quality evidence for gender and NMSS score, low-quality evidence for disease duration, depressive mood, and UPDRS score, and very low-quality evidence for Hoehn-Yahr staging.

**Conclusion:** Normal cognitive function and good mental status are protective factors against PD pain, while female gender, long disease duration, depressive mood, motor dysfunction, high H-Y staging, and severe other non-motor symptoms (sleep disturbance, fatigue) are risk factors. Future high-quality studies with larger samples are needed for further validation.

**Keywords:** Parkinson' s disease; Pain; Non-motor symptoms; Influencing factors; Systematic review

## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer' s disease, clinically manifested by motor symptoms including tremor, bradykinesia, rigidity, and freezing of gait, as well as non-motor symptoms such as pain, constipation, and sleep disturbances. With rapid population aging, its incidence continues to rise. A community-based study in China reported a PD prevalence of 1.37% (95% confidence interval 1.02%-1.73%) among individuals over 60 years, estimating the total number of PD patients in China may reach 3.62 million [1]. Pain is increasingly common in PD patients and represents one of the non-motor symptoms with the greatest impact on quality of life. With numerous clinical pain types and complex manifestations, early identification of pain types, understanding of pain mechanisms, and timely pharmacological or non-pharmacological interventions can help delay disease progression and improve quality of life [2].

Previous studies have explored pain-influencing factors, finding that age, gender, depressive mood, motor symptoms, and disease duration affect pain occurrence and development in PD patients. However, significant heterogeneity exists across studies due to geographical location, population characteristics, sample size, and other factors [3]. Therefore, this study systematically reviews and

analyzes research on factors influencing pain in PD patients to enable early prevention and control of pain risk factors, reduce incidence, and provide clinical references.

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## Methods

### 1.1 Literature Search Strategy

A comprehensive computer-based search was conducted in both Chinese and English databases including CNKI, Wanfang, VIP, CBM, Web of Science, PubMed, MEDLINE, Embase, and The Cochrane Library from inception to April 12, 2022. Chinese search terms included: "Parkinson' s disease/tremor paralysis/pain/risk factors/related factors/influencing factors/predictive factors." English search terms included: "Parkinson' s disease/parkinsonism/ache/pain/douleur/dangerous factor/risk factor/relevant factor/relative factor/correlative factor/impact factor/contributing factor/associated factor/predictive factor/affecting factor." The specific search strategy is shown in Box 1 (using Web of Science as an example).

**Box 1. Literature Retrieval Strategy**

#1 (ALL=(Parkinson' s disease)) OR ALL=(parkinsonism)
#2 (((((((((ALL=(dangerous factor)) OR ALL=(risk factor)) OR ALL=(relevant factor)) OR ALL=(relative factor)) OR ALL=(correlative factor)) OR ALL=(impact factor)) OR ALL=(contributing factor)) OR ALL=(associated factor)) OR ALL=(predictive factor)) OR ALL=(affecting factor)
#3 ((ALL=(ache)) OR ALL=(pain)) OR ALL=(douleur)
#4 #1 AND #2 AND #3

### 1.2 Inclusion and Exclusion Criteria

**1.2.1 Inclusion Criteria:** (1) Patients diagnosed with PD according to diagnostic criteria by attending physicians; (2) Observational studies including cohort, case-control, and cross-sectional studies; (3) Research content focusing on influencing or predictive risk factors for pain in PD; (4) Literature providing data convertible to OR values, 95% confidence intervals, and standard errors.

**1.2.2 Exclusion Criteria:** (1) Non-Chinese or non-English literature; (2) Conference abstracts, reviews, systematic reviews, letters, randomized controlled trials, and animal experiments; (3) Literature with missing data preventing information extraction; (4) Duplicate publications; (5) Literature without full-text availability; (6) Literature conducting only univariate analysis.

### 1.3 Literature Screening and Data Extraction

Two researchers independently screened literature and extracted data, with disagreements resolved through discussion with a third party. After duplicate

removal, titles and abstracts were reviewed for initial screening to exclude obviously irrelevant literature, followed by full-text review according to inclusion and exclusion criteria to determine final inclusion. Extracted data included: first author, publication year, country/region, study type, sample size, pain assessment tools or diagnostic methods, pain incidence, and involved influencing factors.

### 1.4 Quality Assessment of Included Literature

Cross-sectional studies were evaluated using the AHRQ scale [4,5], comprising 11 items scored as "yes" (1 point), "no" or "unclear" (0 points), with final scores of 0-3 indicating low quality, 4-7 moderate quality, and 8-11 high quality. Case-control studies were evaluated using the Newcastle-Ottawa Scale (NOS) [6,7], which assesses three dimensions (eight items): study group selection (4 items), inter-group comparability (1 item), and exposure measurement (3 items).

### 1.5 Statistical Analysis

Descriptive analysis was conducted on all influencing factors, which were tabulated and classified by direction of effect as risk or protective factors. RevMan 5.3 software was used for meta-analysis with subgroup analysis when necessary. Dichotomous variables were expressed as pooled effect sizes using odds ratios (OR) and 95% confidence intervals (CI). Heterogeneity was assessed using $I^2$ statistics: $I^2<50\%$ and $P>0.1$ indicated no or low heterogeneity (fixed-effects model), while $I^2>50\%$ and $P<0.1$ indicated substantial heterogeneity (random-effects model) with sensitivity analysis to explore sources. Funnel plots were generated to assess potential publication bias, with $P<0.05$ considered statistically significant.

### 1.6 Evidence Level Evaluation

The GRADE system was used to evaluate the quality of evidence for pooled effect outcomes, classifying evidence as high, moderate, low, or very low quality. As all included studies were observational, the initial quality level was low. Evaluation criteria included risk of bias, inconsistency, imprecision, indirectness, and other issues (publication bias).

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## Results

### 2.1 Literature Screening Results

The search yielded 1,521 articles. After duplicate removal (n=1,107), title and abstract screening identified 65 articles for full-text review, resulting in 16 included studies [8-23]. The screening process is illustrated in Figure 1 [Figure 1: see original paper]. Publication years ranged from 2008-2022, with a total sample size of 2,855 cases, including 10 Chinese articles [8,10-14,16,20-22]

and 6 English articles [9,15,17-19,23], comprising 11 journal articles [8-10,13,15-19,21,23] and 5 dissertations [11,12,14,20,22].

### 2.2 Basic Characteristics and Quality Assessment of Included Studies

Among the 16 studies, 14 were cross-sectional and 2 were case-control, involving 24 influencing factors including gender, age, and disease duration (Table 1 ). Nine studies were rated as high quality and 7 as moderate quality (Tables 2 and 3 ).

**Table 1. General Characteristics of Studies on Factors Affecting Pain in PD Patients**

| Study | Year | Country/Region | Study Type | Sample Size | Pain Assessment Tool/Diagnostic Method | Pain Incidence | Influencing Factors |
|---|---|---|---|---|---|---|---|
| Guo Zhiying [8] | 2022 | China | Case-control | 120 | UPDRS II item 17 | 45.8% | A, C, D, E, F, G, H |
| Li Jun [9] | 2022 | China | Cross-sectional | 200 | International Association for the Study of Pain criteria | 62.5% | C, K, F |
| Xing Fengbo [10] | 2021 | China | Cross-sectional | 150 | NRS | 66.7% | A, F, H, L |
| Tang Jia [11] | 2021 | China | Cross-sectional | 81 | Brief Pain Questionnaire | 65.4% | A, F, H, L |
| Li Xiaohan [12] | 2021 | China | Cross-sectional | 100 | VAS | 53.0% | C, F, G, H |
| Sun Haihua [13] | 2020 | China | Case-control | 60 | VAS | 58.3% | A, F, M, X |
| Liu Yudong [14] | 2020 | China | Cross-sectional | 120 | Short Form (SF) | 55.8% | A, F, M, S |
| Pritha G [15] | 2020 | Italy/USA | Cross-sectional | 450 | KPPS, BPI | 83.1% | F, V, W |

| Study | Year | Country/Region | Study Type | Sample Size | Pain Assessment Tool/Diagnostic Method | Pain Incidence | Influencing Factors |
|---|---|---|---|---|---|---|---|
| Li Yao [16] | 2019 | China | Cross-sectional | 100 | VAS | 61.0% | A, F, T, U |
| Conrad J [17] | 2019 | Australia | Cross-sectional | 82 | VAS | 70.7% | A, F, H, L |
| Mayela R [18] | 2017 | Mexico | Cross-sectional | 121 | Brief Pain Questionnaire, McGill Pain Questionnaire | 41.3% | A, C, D, E, F, G, H |
| Erhan A [19] | 2017 | Turkey | Cross-sectional | 105 | VAS | 62.9% | C, Q, R |
| Zhang Xiaoyi [20] | 2014 | China | Cross-sectional | 60 | VAS | 68.3% | A, F, H, L |
| Yang Fen [21] | 2014 | China | Cross-sectional | 120 | VAS | 52.5% | A, F, H, L |
| Dai Yuntao [22] | 2012 | China | Cross-sectional | 86 | VAS | 60.5% | A, F, H, L |
| Laurence N [23] | 2008 | France | Cross-sectional | 100 | VAS | 58.0% | A, F, H, L |

*Note: A=Gender, B=Age, C=Disease duration, D=MMSE score, E=MoCA score, F=Depressive mood, G=UPDRS score, H=Hoehn-Yahr staging, I=Levodopa equivalent daily dose (LEDD), J=FS-14 score, K=PDSS-2 score, L=Raphe nucleus echo changes, M=NMSS score, N=PSQI sleep quality score, O=Pain-prone medical conditions, P=UPDRS motor complications, Q=Balance, R=Health-related quality of life, S=Motor subtype, T=UPDRS Part II, U=Rigidity, V=Age at onset, W=Motor fluctuations, X=Cardiovascular disorders; UPDRS=Unified Parkinson' s Disease Rating Scale, NRS=Numerical Rating Scale, KPPS=King' s Parkinson' s Disease Pain Scale, VAS=Visual Analogue Scale, MMSE=Mini-Mental State Examination, FS-14=Fatigue Scale, NMSS=Non-Motor Symptoms Scale.*

### 2.3 Descriptive Analysis of Pain Influencing Factors in PD Patients

The 16 studies involved 24 influencing factors. Risk factors for PD pain included female gender, elderly patients, long disease duration, high Hoehn-Yahr staging, young onset age, high levodopa equivalent daily dose, cardiovascular disorders, abnormal raphe nucleus echo changes, high depressive mood, high UPDRS / scores, presence of motor complications, high FS-14 score (severe fatigue), PDSS-2 score, high PSQI sleep quality score (sleep disturbance), high NMSS score, presence of PD-related motor subtypes, motor fluctuations, rigidity, pain-prone medical conditions, poor balance, and poor health-related quality of life. Protective factors included high MMSE score and high MoCA score (Table 4 ).

### 2.4 Meta-Analysis of Pain Influencing Factors in PD Patients

Among the 16 studies, meta-analysis could be performed on six influencing factors: gender, disease duration, depressive mood, UPDRS score, Hoehn-Yahr staging, and NMSS score.

**2.4.1 Gender:** Seven studies [8,9,12,15,18,19,22] reported gender as an influencing factor. Heterogeneity test showed P=0.005 (<0.01) and $I^2$=68% (>50%), indicating a random-effects model should be used. Results showed female gender was a risk factor for pain in PD patients [OR=3.73, 95%CI (1.75,7.96), P=0.0007] (Figure 2 [Figure 2: see original paper]).

**2.4.2 Disease Duration:** Three studies [8,11,17] reported disease duration affected pain occurrence. Heterogeneity test showed P=0.17 (>0.1) and $I^2$=44% (<50%), indicating a fixed-effects model. Results showed long disease duration was a risk factor [OR=1.35, 95%CI (1.15,1.60), P=0.0003] (Figure 3 [Figure 3: see original paper]).

**2.4.3 Depressive Mood:** Ten studies [8,12,13,16,18-21,23] reported depressive mood affected pain occurrence. Due to different assessment tools, subgroup analysis was performed. Heterogeneity test showed P=0.01 (<0.1) and $I^2$=57% (>50%), indicating a random-effects model. Results showed depressive mood was a risk factor [OR=1.14, 95%CI (1.07,1.22), P<0.0001] (Figure 4 [Figure 4: see original paper]).

**2.4.4 UPDRS Score:** Three studies [8,13,21] reported UPDRS score affected pain occurrence. Heterogeneity test showed P=0.38 (>0.1) and $I^2$=0% (<50%), indicating a fixed-effects model. Results showed motor dysfunction was a risk factor [OR=1.07, 95%CI (1.03,1.11), P=0.0002] (Figure 5 [Figure 5: see original paper]).

**2.4.5 Hoehn-Yahr Staging:** Three studies [8,12,13] reported Hoehn-Yahr staging as an influencing factor. Heterogeneity test showed P=0.14 (>0.1) and $I^2$=50%, indicating a fixed-effects model. Results showed high Hoehn-Yahr staging was a risk factor [OR=2.28, 95%CI (1.28,4.04), P=0.005] (Figure 6 [Figure 6: see original paper]).

**2.4.6 NMSS Score:** Two studies [15,18] reported high NMSS scores as an influencing factor. Heterogeneity test showed P=0.24 (>0.1) and $I^2$=20% (<50%), indicating a fixed-effects model. Results showed severe non-motor symptoms were a risk factor [OR=1.68, 95%CI (1.46,1.93), P<0.00001] (Figure 7 [Figure 7: see original paper]).

### 2.5 Publication Bias Assessment

Sensitivity analysis identified two studies [24,25] as major sources of heterogeneity. Funnel plot analysis showed symmetrical distribution, indicating no significant publication bias (Figure 8 [Figure 8: see original paper]).

### 2.6 GRADE Quality Assessment

GRADE evaluation of pooled effect outcomes showed "gender" and "NMSS score" as moderate-quality evidence, "disease duration," "depressive mood," and "UPDRS score" as low-quality evidence, and "Hoehn-Yahr staging" as very low-quality evidence (Table 5 ).

**Table 5. GRADE Evidence Quality Evaluation of Included Literature**

| Outcome Indicator | Relative Effect (95% CI) | Quality Level | Downgrading Factors |
|---|---|---|---|
| Gender | 3.73 (1.75,7.96) | Moderate | Serious bias |
| Disease Duration | 1.35 (1.15,1.60) | Low | Serious bias , Serious imprecision |
| Depressive Mood | 1.14 (1.07,1.22) | Low | Serious bias , Serious imprecision |
| UPDRS Score | 1.07 (1.03,1.11) | Low | Serious bias , Serious imprecision |
| Hoehn-Yahr Staging | 2.28 (1.28,4.04) | Very Low | Serious bias |
| NMSS Score | 1.68 (1.46,1.93) | Moderate | Serious bias |

*Note: Subjective outcome measurement, incomplete follow-up; $I^2$>50%; Narrow confidence interval width.*

## Discussion

This systematic review included 16 studies (14 cross-sectional, 2 case-control) with 9 high-quality and 6 moderate-quality studies, yielding relatively credible meta-analysis results.

### 3.1 Higher Pain Incidence in Female PD Patients

Female PD patients showed higher pain incidence. Previous research indicates gender is a key factor affecting PD development, with women experiencing faster pain progression and different pain pathophysiology [26,27]. Possible reasons include enhanced pain sensitivity in female PD patients, decreased estrogen and progesterone levels in postmenopausal women leading to more complex perception and cognition, and greater attention to symptom changes [28-30]. Animal studies show microglial activation inhibitors produce pain reversal only in male mice [31]. Additionally, female patients have lower musculoskeletal mass, and musculoskeletal pain represents a major pain type in PD, predominantly affecting women [17].

Heterogeneity existed among included studies. Sensitivity analysis identified Pritha G et al. [15] as the main source. Potential reasons include: (1) Different diagnostic criteria (2015 MDS criteria vs. UK Parkinson's Disease Society Brain Bank criteria); (2) Population differences (dual-center international study from Italy/USA with geographic, racial, and cultural variations) [32,33]; (3) Use of two pain assessment tools (KPPS and BPI) versus single tools in other studies. Since pain significantly impacts quality of life and correlates with female gender, future treatment should emphasize physiological and psychosocial care for female patients.

### 3.2 Long Disease Duration Increases Pain Risk

Long disease duration was identified as a risk factor. Previous studies show longer PD duration correlates with more severe and frequent pain, progressing toward multimodal distribution [34]. The mechanism may involve excessive consumption of dopamine and glutamate in basal ganglia, increased dopaminergic neuron apoptosis, and over-inhibition of thalamic activity causing myotonic pain [35]. Clinicians should pay special attention to long-duration PD patients, thoroughly assess pain history, identify pain types, and select appropriate interventions.

### 3.3 Higher Depressive Mood Increases Pain Risk

Depressive mood was a significant risk factor. The association between depression and pain has been consistently strong, with pain severity and disability directly correlating with depression [36,37]. The mesolimbic dopaminergic system plays an important role in pain by delivering dopamine to structures like the prefrontal cortex and amygdala, which control emotion and pain modulation [38]. Depressed patients show amygdala dysfunction that can trigger pain [39]. Animal studies demonstrate bidirectional effects where depressive behavior induces persistent hyperalgesia and vice versa [40].

Heterogeneity was primarily attributed to Mayela R et al. [18], likely due to different depression assessment tools. While Mayela R used NMSS subscale scores and Erhan A used DSM-IV criteria, other studies used HAMD or HADS-D,

which show high accuracy and sensitivity for depression [41]. Clinicians should closely monitor PD patients with depression and provide early intervention to prevent pain development.

### 3.4 Severe Motor Dysfunction Increases Pain Risk

High UPDRS scores indicated motor dysfunction as a risk factor. Studies show pain may be amplified by accompanying motor dysfunction, with pain symptoms fluctuating more frequently during "off" periods [42,43]. Motor dysfunction may increase pain sensitivity through central pathway sensitization affecting pain pathways, increased neural substrate activity, and lowered pressure pain thresholds [44]. Rigidity shows the strongest association with pain due to altered body mechanics and posture causing musculoskeletal pain [45]. Earlier studies found bradykinesia and freezing of gait cause pain, while tremor shows no association [46]. Clinicians should 特别关注 patients with severe gait disorders and rigidity, incorporating functional exercises to alleviate pain.

### 3.5 Higher Hoehn-Yahr Staging Increases Pain

High Hoehn-Yahr staging was a risk factor. As Hoehn-Yahr staging evaluates clinical motor symptoms, higher stages indicate more severe limb involvement and motor symptoms, leading to stronger central sensitization and corresponding with motor dysfunction findings.

### 3.6 Severe Non-Motor Symptoms Increase Pain Risk

High NMSS scores indicated severe non-motor symptoms as a risk factor, encompassing depression, sleep disturbance, and fatigue. Approximately 80% of PD patients with pain have sleep disturbances, showing high correlation [47]. Conversely, severe negative emotions and poor quality of life increase pain risk [48]. Non-dopaminergic structures mediating spinal cord, brainstem, and limbic system degeneration may cause pain related to brainstem or non-dopaminergic neurotransmitter abnormalities [49]. Early identification and intervention for non-motor symptoms are clinically important to prevent disease progression.

### Limitations

This study has several limitations: (1) The search did not combine subject headings with free terms, potentially missing relevant literature; (2) Most included studies were cross-sectional, limiting assessment of causality and continuity; (3) Although many influencing factors were identified, they were dispersed across studies, with only six common factors available for meta-analysis.

## Conclusion

This systematic review identified female gender, long disease duration, high depressive mood, severe motor dysfunction, high Hoehn-Yahr staging, and severe other non-motor symptoms as risk factors for pain in PD patients, while normal cognitive function and good mental status were protective factors. Clinicians should closely monitor female patients, those with long disease duration, and those with severe motor and non-motor symptoms (negative emotions, sleep disturbance, fatigue), strengthening early pain assessment and screening to identify risk factors and effectively control pain incidence. Future large-sample, multicenter studies are needed to further clarify pain risk and protective factors, establish PD pain risk prediction models, and implement preventive clinical interventions to improve quality of life and delay disease progression.

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## Author Contributions

Zhang Yutong and Xu Guihua conceived and designed the study, analyzed and interpreted results. Zhang Yutong and Wang Qiuqin collected and organized data. Zhang Yutong, Xu Yuchen, Weng Heng, Liang Yongqi, and Wang Lulu performed statistical analysis. Zhang Yutong drafted the manuscript. Wang Qing revised the manuscript. Wang Qiuqin and Wang Qing controlled quality and reviewed the manuscript. Xu Guihua supervised the overall project.

**Conflicts of Interest:** None declared.

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