

## Psychological Factors and Pain Exacerbation in Knee Osteoarthritis: A Web Based Case-Crossover Study

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### Abstract

**Objectives:** The pain experienced by osteoarthritis (OA) patients is neither constant nor unchanging and patients experience episodes of pain exacerbations. Using an innovative web based case-crossover design, we evaluated whether psychological factors are risk factors for pain exacerbations in patients with knee OA.

**Methods:** In a 3-months internet-based case-crossover study, participants with symptomatic knee OA were recruited and followed at 10-day intervals (control periods). Participants were also instructed to log on to the study website if they experienced a knee pain exacerbation (case periods). Pain exacerbation was defined as an increase of  $\geq 2$  on a participant's numerical rating scale (0-10) from his/her usual background pain score reported at baseline visit. The periods were 10 days for affect measures and 30 days for pain coping/perceived stress measures. The relation of psychological factors to the risk of pain exacerbation was examined using conditional logistic regression.

**Results:** Of 298 participants recruited, 149 and 54 provided both case and control periods with no overlap for examining affect and pain coping/perceived stress factors respectively. Higher negative affect (negative affect score  $\geq 18$ : odds ratio (OR) 6.49; 95% CI 3.45-12.2) and passive coping strategies (OR 1.26; 95% CI 1.05-1.50) were associated with increased risk of pain exacerbations; while higher active coping strategies (OR 0.81; 95% CI 0.66-0.98) had a protective effect.

**Conclusion:** The findings emphasize the need for avoidance of negative affect and passive pain coping strategies and conversely reinforce the benefit of active pain coping strategies in prevention and management of OA pain exacerbations.

**Keywords:** Knee osteoarthritis; Psychological factors; Pain exacerbation; Case-crossover study; Web based

### Introduction

Osteoarthritis (OA) is a leading cause of disability worldwide, largely due to pain, the primary symptom of the disease [1,2]. The source of pain is not well understood and is best framed within a bio-psycho-social framework, which posits that biologic, psychological, and social factors all play a significant role in OA pain [3,4].

While pain in knee OA is considered to be chronic, the pain experienced by OA patients is neither constant nor unchanging. Patients often feel intermittent increases in pain intensity that are typically of a relatively short duration, and best described as pain exacerbations [4-7]. If the potential risk factors for these pain exacerbations could be identified and avoided, many such episodes could be prevented or minimized.

Evidence supports the important role of psychological factors in understanding OA pain [3,4,8-10], however their triggering role in recurrent OA pain exacerbations remains unclear.

Prior studies [5,9-17], have examined the relationship between specific psychological variables (e.g. coping strategies, mood, catastrophizing) and pain variation in OA. However these studies including most recent diary-based studies [5,11,14] have several limitations. First, they have largely focused on the relationship of psychological factors to pain variability across individuals with different characteristics (e.g. different racial background) and across particular time points (e.g. of the week or day). Therefore, a comparison of intermittent and transient exposures during defined time periods within an individual has not been fully addressed. Second, pain variability has been measured by either focusing on the range of pain scores or average pain scores and not as recurrent pain attacks or exacerbations. Third, their design did not allow them to fully control for confounders that are constant over time within

individuals. Fourth, they are unable to establish cause-effect relationship that might provide insights into whether psychological factors precede pain exacerbations in OA.

Therefore, to overcome these limitations we aimed to evaluate the effects of potential psychological precipitating factors including pain coping strategies, positive or negative affect and perceived stress on recurrent pain exacerbations in knee OA using an innovative web based case-cross over study.

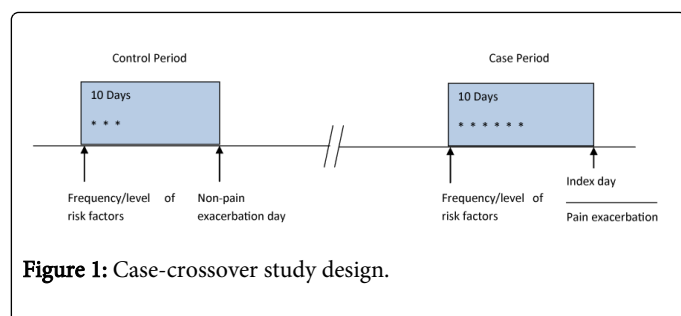
## Methods

### Study design

We conducted an internet-based case-crossover study. The case-crossover design uses each participant (case) as his/her own control and is best suited [18-21] to assess effects of transient and intermittent exposures (triggers) on acute events (e.g. pain flares). It specifically compares the frequency of risk factors occurring during the period right before participant experiences pain exacerbation (case period) with the period when the same participant did not experience pain exacerbation (control period) [18-21].

In addition, our study used a web-based design. The Internet is an efficient tool to collect data and allowed us to capture both exposure and outcome in real time [21]. Participants were followed for 3 months and asked to complete online questionnaires at 10-day intervals (control periods). Participants were also instructed to log on to the website and complete the questionnaires any time they experienced a knee pain exacerbation (case periods). Pain exacerbation was defined for patients and confirmed via the website as an increase of  $\geq 2$  on a participant's numerical rating scale (NRS) (0-10) [22] from his/her usual background pain score reported at the baseline visit and lasting for a minimum of 8 hours.

The frequency/level of each potential psychological risk factor occurring during the case periods was then compared with that occurring during the control periods (Figure 1).



### Participant recruitment

A password protected website was constructed and located on a secure server. The website provided study information, administered a screening questionnaire, displayed a consent form, and administered the exposure and pain assessment questionnaires.

Participants were recruited from existing databases (at Royal North Shore Hospital and University of Melbourne) of persons who had been screened for or participated in previous knee OA studies and had expressed willingness to participate in future studies. In addition to this source we recruited new community volunteers through Google and Facebook advertisements.

Eligible participants were required to: (1) be aged  $\geq 40$  years; (2) have knee pain on most days (5-7 days/week); (3) have at least one knee meeting the American College of Rheumatology (ACR) Criteria for knee OA [23]; (4) have definite tibiofemoral (Kellgren and Lawrence Grade (KLG) [24]  $\geq 2$ ); or patellofemoral OA on a radiograph; (5) have no plans for a total knee replacement in symptomatic knee(s) within the next 6 months and no history of total knee replacement of the most painful knee; (6) have no history of secondary OA (inflammatory, osteonecrosis, etc.); (7) have an active e-mail account and access to the internet; and (8) have good understanding of spoken and written English.

This study was approved by the Human Ethics Committees of the Universities of Sydney and Melbourne.

### Study questionnaires

Participants were asked to complete the following questionnaires online during the study period:

1) **Demographic questionnaire** (age, sex, race, etc.) asked at baseline visit.

2) **Control-period questionnaire:** to assess the exposure to potential psychological risk factors during the periods without pain exacerbation. These questionnaires were administered every 10 days for affect and every 30 days for pain coping strategies and perceived stress, in accordance with the intervals in the validated psychological questionnaires used for the study.

3) **Case-period questionnaire:** to assess the exposure to potential psychological factors over periods prior to the pain exacerbation. These questionnaires were the same as the control period questionnaires but given at the time of pain exacerbation.

4) **Knee pain exacerbation questionnaire (outcome measurement):** to measure pain exacerbation via a numerical rating scale (NRS 0-10) [22]. Participants were instructed at baseline and via regular email reminders to log in to the study website and complete this questionnaire immediately if they experienced a pain exacerbation. Participants who reached the exacerbation threshold were then directed to complete the case-period questionnaire.

5) **Psychological factors questionnaires (exposure measurements):** The following psychological variables were assessed and scored using validated questionnaires.

### Pain coping strategies

1) Pain coping inventory (PCI) questionnaire

PCI measures the items of active (e.g. engaging in physical exercise) and passive (e.g. restricting social activities,) coping strategies [25].

2) Daily pain coping strategies questionnaire

In this questionnaire [26] the items of problem-focused coping (e.g. relaxation) and emotion-focused coping (e.g. seeking emotional support) were asked.

3) Pain catastrophizing questionnaire

Pain catastrophizing was assessed on a subscale from the coping strategies questionnaire (CSQ) [27].

4) Coping strategy effectiveness questionnaire

The perceived effectiveness of participant’s coping strategies (e.g. ability to gain control over pain) was assessed on a scale from the CSQ [27].

**Positive and negative affect**

Positive and negative affect schedule (PANAS) questionnaire

The adjectives assessing negative affect (e.g. distressed, upset) and positive affect (e.g. excited, strong,) were used to rate one’s affect [28].

**Perceived stress**

Perceived stress scale (PSS) questionnaire

This [29] measures the degree to which situations in one’s life are appraised as stressful.

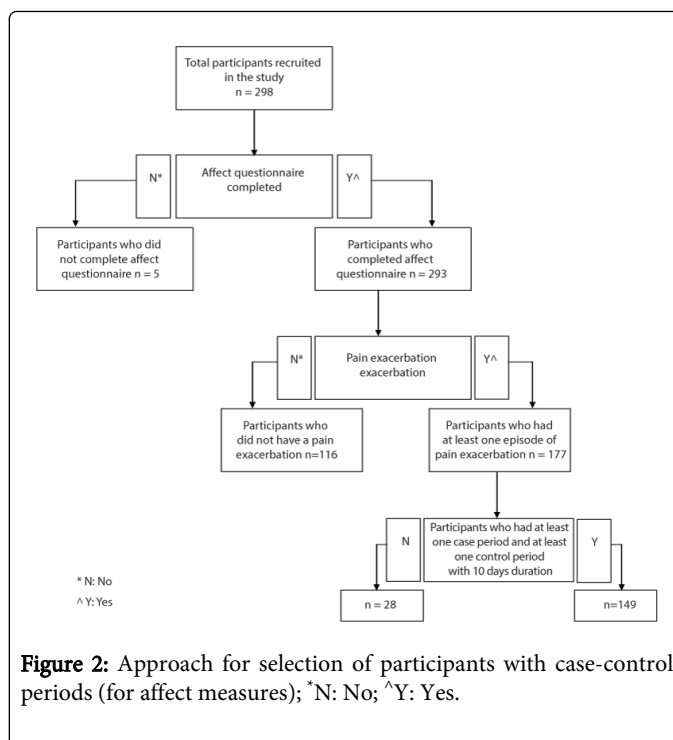
**Statistical analysis**

Descriptive statistics were used for all study participants as well as for those with case-control periods. We assessed the relationship of psychological factors (predictive variables) to the risk of knee pain exacerbation (outcome variable) using conditional logistic regression (SAS 9.4). Only participants with case-control periods were included in the regression analysis. Case-crossover design is analogous to a matched retrospective case-control design in which only matched pairs that are discordant for exposure contribute to the information [18-20]. As case-crossover design is a self-matched design [18-21], therefore we did not require adjusting for the independent risk factors which are unchanged within a person such as Body Mass Index (BMI), age, sex.

The analysis for participants with case-control periods was performed in two sub-groups: 1) affect measures sample and 2) pain coping/PSS measures sample. This categorization was based on the intervals questioned in these measures (10 days for affect and 30 days for pain coping/PSS), which led to two samples size of N=149 for affect measures and N=54 for pain coping/PSS measures.

**Selection procedure of the participants with case-control periods:**

The selection approach of the participants with case-control periods for affect measures is demonstrated in Figure 2. Of 298 total participants recruited in the study, 293 participants completed mood questionnaires and 177 of them had experienced at least one episode of pain exacerbation. Of those 177 participants who had a pain exacerbation, 149 participants had at least one case period and at least one control period of 10 days duration with no overlap between case and control periods (Figure 2).



**Figure 2:** Approach for selection of participants with case-control periods (for affect measures); \*N: No; ^Y: Yes.

A similar approach was used for pain coping and perceived stress measures. 54 participants had at least one case period and at least one control period of 30 days duration with no overlap between case and control periods.

**Results**

**Demographic characteristics of participants**

The detailed demographic characteristics of all study participants as well as participants with case-control periods for affect measures (N=149) (Women: 66 %, mean age: 62.1 ± 8.1 years, mean BMI: 30.0 ± 6.5, Caucasian: 92%, education more than high school: 60%) and participants with case-control periods for pain coping/PSS measures (N=54) (Women: 65%, mean age: 62.7 ± 9.0, mean BMI: 30.5 ± 6.3, Caucasian: 96%, education more than high school: 62%) have shown in Table 1.

	All study participants	Participants with case-control periods (for affect measures)	Participants with case-control periods (for coping and PSS measures)
Characteristics	(N=298)	(N=149)	(N=54)
Age (years), mean (sd)	62.1(8.1)	62.1(8.1)	62.7(9.0)
Female, n (%)	183(61)	98(66)	35(65)
BMI* (kg/m <sup>2</sup> ), mean (sd)	29.7(6.2)	30.0(6.5)	30.5(6.3)
Race*, n (%)			
Caucasian	271(92)	135(92)	50(96)

Asian	13(4)	5(3)	0(0)
Others	10(3)	7(5)	2(4)
Education Level <sup>†</sup> , n (%)			
<Less than high School	50(17)	27(18)	10(19)
=Completed high School	59(20)	32(22)	10(19)
>Higher than high School	187(63)	89(60)	33(62)
KOOS <sup>‡</sup> , mean (sd)			
Symptoms	44.5(13.0)	44.8(14.0)	42.6(13.8)
Pain	55.6(16.6)	54.7(15.8)	52.9(14.9)
Function-daily living	62.6(19.3)	61.6(19.6)	59.7(18.2)
Function-sport/recreation	22.3(23.2)	22.7(24.0)	20.7(24.8)
Quality of life	40.4(18.2)	39.8(17.7)	38.9(15.9)
No. Comorbidities <sup>§</sup> , n (%)			
≤ 1	126 (42)	66 (44)	18 (33)
2-4	159 (54)	75 (50)	33 (61)
≥ 5	12 (4)	8 (5)	3 (6)
*Number of participants with missing value: body mass index 17; race 4; education level 2; KOOS 1; comorbidities 1			
†Intermittent and constant osteoarthritis pain (ICOAP) score			
‡Knee injury and osteoarthritis outcome score (KOOS)			

**Table 1:** Baseline demographic characteristics of study participants.

### Psychological characteristics of participants

The baseline psychological characteristics of all study participants as well as participants with case-control periods (for both affect and coping/PSS sub-groups) are shown in Table 2. These results show that our participants had a relatively good psychological status at baseline as demonstrated by higher positive affect and active/problem-focused

pain coping scores and lower negative affect, passive/emotion-focused pain coping and perceived stress scores.

The demographics (Table 1) and baseline psychological characteristics (Table 2) of the participants with case-control periods were similar to the overall group.

	All study participants	Participants with case-control periods (for affect measures)	Participants with case-control periods (for pain coping and PSS measures)
Characteristics	(N=298)	(N=149)	(N=54)
<b>Affect</b>			
Positive affect score (10-50)	33.7(8.0)	34.2(8.1)	33.2(8.2)
Negative affect score (10-50)	16.5(6.4)	16.5(6.5)	16.3(5.9)
<b>Pain Coping Strategies</b>			
PCI-passive coping (0-24)	8.1(4.8)	8.1(4.7)	9.0(4.2)
PCI-active coping (0-20)	12.2(3.6)	12.4(3.8)	12.0(3.7)
All coping strategies (0-7)	3.4(1.8)	3.5(1.8)	3.7(1.8)
Problem-focused (0-3)	2.2(1.0)	2.3(1.0)	2.4(0.9)

Emotion-focused (0-4)	1.2(1.1)	1.2(1.2)	1.2(1.2)
Pain catastrophizing (0-2)	0.3(0.7)	0.3(0.7)	0.2(0.5)
Control over pain (0-6)	3.4(1.4)	3.5(1.4)	3.4(1.2)
Ability to decrease pain (0-6)	3.1(1.4)	3.2(1.4)	3.2(1.5)
Overall coping strategy effectiveness (0-12)	6.5(2.6)	6.8(2.6)	6.6(2.5)
<b>Perceived Stress Scale</b>			
PSS (0-40)	13.7(6.9)	13.7(6.8)	13.6(6.3)

**Table 2:** Baseline psychological characteristics of study participants.

### Association between psychological factors and pain exacerbation

**Relation of negative and positive affect to the risk of pain exacerbation (N=149):** The results in Table 3 show that higher negative affect scores were associated with a significant increased risk of a pain exacerbation with OR 2.77 (95% CI 1.74, 4.39) for negative affect scores of 13-17 and OR 6.49 (95%CI 3.45, 12.2) for negative affect scores  $\geq 18$  respectively. However, no such an association was observed for the positive affect scores (OR 1.03, 95% CI 0.99, 1.07).

	Odds Ratio (95% CI)	P
<b>Affect*</b>		
Positive affect score (10-50)	1.03(0.99, 1.07)	0.19
Negative affect score (10-50)		<0.001
10-12	1.00	
13-17	2.77(1.74, 4.39)	
$\geq 18$	6.49(3.45, 12.2)	
<b>Pain Coping Strategies<sup>^</sup></b>		
PCI-passive coping (0-24)	1.27(1.06, 1.51)	0.009
PCI-active coping (0-20)	0.83(0.69, 1.00)	0.05
All coping strategies (0-7)	0.91(0.65, 1.26)	0.56
Problem-focused coping (0-3)	0.97(0.58, 1.61)	0.90
Emotion-focused coping (0-4)	0.75(0.40, 1.39)	0.36
Pain catastrophizing (0-2)	1.96(0.60, 6.39)	0.27
Control over pain (0-6)	0.65(0.39, 1.09)	0.10
Ability to decrease pain (0-6)	0.73(0.46, 1.16)	0.18
Overall coping strategies effectiveness (0-12)	0.74(0.54, 1.01)	0.06
<b>Perceived Stress Scale (PSS)<sup>^</sup>(0-40)</b>	0.97(0.86, 1.10)	0.65

\*For affect measures (positive and negative affect scores), 149 participants who had both case and control periods provided data for regression analysis.

<sup>^</sup>For pain coping and PSS measures, 54 participants who had both case and control periods provided data for regression analysis.

**Table 3:** Association between psychological factors and pain exacerbation by conditional logistic regression analyses.

**Relation of pain coping strategies and perceived stress to the risk of pain exacerbation (N=54):** Higher passive coping strategies scores were associated with the risk of a pain exacerbation with OR 1.27 (95% CI 1.06, 1.51). In contrast, higher active coping strategies scores had a protective effect from pain exacerbation with OR 0.83 (95% CI 0.69, 1.00).

There was a weak protective effect of higher overall coping strategies effectiveness scores on the risk of a pain exacerbation with OR 0.74 (95% CI 0.54, 1.01).

There was no apparent association between problem-focused and emotion-focused coping and pain exacerbations. ORs of pain exacerbation were 0.97 (95% CI 0.58, 1.61) for problem-focused coping and 0.75 (95% CI 0.40, 1.39) for emotion-focused coping, respectively. Similarly, neither pain catastrophizing nor higher perceived stress was associated with pain exacerbation (Table 3).

### Discussion

This study showed a significant and likely clinically important predictive association between negative affect and OA pain exacerbations in the sample of 149. While the use of passive coping strategies increased the risk of OA pain exacerbations, the use of active coping was associated with a protective effect in the sample of 54.

These results support the study hypothesis that psychological factors are important in predisposing to pain exacerbations in persons with knee OA.

The significant relationship of higher negative affect scores to the increased risk of pain exacerbations in the sample of 149 supports the association between OA pain and low mood/depression shown in previous studies [30-40] and important role of depression as a predictive factor for OA treatment outcomes such as pain and function [34,37,39,40]. However, these studies have largely focused on the association between chronic OA pain and depressive/low mood as well as the effect of chronic pain on the increased risk of depression rather than the predictive effect of low mood on acute pain exacerbations as examined in our study. In addition, the relationship of higher negative affect scores to pain exacerbation underscores the



importance of fluctuations of negative affect as a short-term transient risk factor [28,30,35].

Our findings also support the relationship between using a particular pain coping strategy and the intensity of pain demonstrated in other studies [4,10,11,16,17]. In the sample of 54, we showed that greater use of passive coping strategies was associated with an increased risk of pain exacerbation whereas greater use of active coping strategies was associated with a reduction in risk.

The relation between using passive coping strategies and increased pain is explained by the fact that such strategies are associated with poorer adjustment to the level of pain [41,42]. We did not find a relation between emotion focused and problem focused coping strategies and pain exacerbation, which could, in part, be explained by the small sample size (N=54) used for coping measures with inadequate power to detect a relationship between these factors.

Our study also showed a weak association between greater effectiveness of coping strategies and decreased risk of pain exacerbation in the sample size of 54. This supports the results of previous studies emphasizing the importance of one's coping efficacy in controlling arthritis pain [4,27,41-43].

Although pain catastrophizing is known to relate to OA pain [8,12], in this study there was no significant association between pain catastrophizing and risk of pain exacerbation in the sample of 54. This result was consistent with the finding from another study [11], which found no association between pain catastrophizing and daily pain. This could be explained by the understanding that catastrophizing is considered a trait and does not change or fluctuate over time [44].

Previous studies [36,38,45] have shown increased perceived stress level among OA patients with chronic pain. Despite this, we found no association between perceived stress and pain exacerbations in the sample of 54. A possible explanation is that perceived stress was measured in a small sample (N=54 as pain coping) with inadequate power to detect this relationship.

Several characteristics of our study are noteworthy. First, studying the triggering effect of psychological factors especially those transient factors (e.g. affect) on the risk of pain exacerbations is challenging [46]. We applied two innovative approaches, a case-crossover study design and use of the Internet. In a case-crossover design, self-matching of each participant eliminates bias in control selection and self-confounding removes confounding effects of factors that are constant over time within individuals but differ among study participants (e.g. age, genetics, race, education) [18-21].

Second, using the Internet was a convenient and accessible tool for participants as shown by the high rate of study completion (98%). Further, we showed that both risk factors and disease occurrence could be assessed in real time, which should minimize the potential recall bias.

Third, by ensuring that there was no overlap between case and control intervals and using defined intervals, we decreased the confounding as well as carry over effect of a pain exacerbation in the following period on the psychological status of participants. This enhances the causality effect of psychological factors on the pain exacerbation and decreases the possibility of reverse causality, which were limitations in prior studies [5,10-14,35].

Our study has some limitations. All pain coping strategies and PSS were assessed every 30 days due to the interval (30 days) in the original

validated questionnaires used in our study. This led to a smaller sample (subgroup) of participants (N=54) with both case and control periods of 30 days duration with no overlap. Due to this, we were not able to show stronger associations between different coping strategies/PSS and risk of pain exacerbations. This should be considered in future studies by choosing psychological instruments with shorter intervals to increase the sample size while still avoiding the overlap between intervals.

While our participants were from all Australian states, there is a strong possibility that those with higher education level or socioeconomic status participated considering the study eligibility criteria (e.g. access to internet and email account, good understanding of English). In addition, there was a high proportion of Caucasians (more than 90%). Therefore, the findings may not be generalizable to all knee OA patients.

Participants were asked to retrospectively recall the risk factors and hence there is possibility for recall bias. In addition, although participants were prompted to log in online immediately when they experienced a pain exacerbation, there is the potential for under-reporting of pain exacerbations. This could be surveyed in future studies by asking participants the number of pain exacerbations that they did not report to study website.

Lastly, there is the possibility of a confounding effect of other time-varying potential risk factors on knee OA pain exacerbation (such as medication use or physical activity). Therefore, these factors should be considered in future analysis as independent risk factors.

Identifying the potentially modifiable psychological risk factors for pain exacerbation in knee OA has important clinical implications given the paucity of safe and effective treatments for OA pain and the high proportion of OA patients with persistent pain and functional limitation despite therapy [43].

Further research to better elucidate these relationships will be important, as psychological wellbeing is clearly a modifiable component of health and may represent an important new avenue for prevention and treatment of OA pain exacerbations by directing psychological interventions such as pain coping skills training (PCST) protocols (e.g. involving pain education and training in skills such as relaxation, activity pacing, problem solving) [8], emotional disclosure (e.g. writing or talking about thoughts or feelings related to pain) [47] as well as other self-management strategies (e.g. self-monitoring, training in self-reinforcement, and maintenance training) used in cognitive behavior therapy [48].

## Conclusion

The findings demonstrate that in OA patients an emphasis should be made on avoidance or minimization of negative affect and passive pain coping strategies use in prevention and management of OA pain exacerbations. Conversely, reinforcement on use of active pain coping will be important in controlling OA pain exacerbations.

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## Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

## Authors' Contributions

TE drafted the manuscript. TE revised different versions of manuscript and finalized it based on authors' comments. TE contributed to the conception of methodology of the study.

JC, TE and YZ, DJH contributed to statistical methodology and data analysis.

TE, FK, KB, JC, LM, DJH interpreted the findings.

Acquisition of data was via Internet.

JM and BM contributed to the recruitment and database management.

DJH had full access to all the data in the study and takes full responsibility for the integrity of the data and the integrity of work as a whole.

DJH conceived the study and DJH, KB, LM, YZ contributed to the design and conduct of the study.

TE, FK, KB, JC, LM, AW, YZ, DJH critically revised the manuscript.

All authors reviewed and approved the final version of manuscript to be submitted for publication.

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