

Prevalence of mental health disorders in inflammatory bowel disease: an Australian outpatient cohort

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Background: This study aimed to characterize prevalence of anxiety and depressive conditions and uptake of mental health services in an Australian inflammatory bowel disease (IBD) outpatient setting.

Methods: Eighty-one IBD patients (39 males, mean age 35 years) attending a tertiary hospital IBD outpatient clinic participated in this study. Disease severity was evaluated according to the Manitoba Index. Diagnosis of an anxiety or depressive condition was based upon the Mini-International Neuropsychiatric Interview and the Hospital Anxiety and Depression Scale.

Results: Based on Hospital Anxiety and Depression Scale subscale scores >8 and meeting Mini-International Neuropsychiatric Interview criteria, 16 (19.8%) participants had at least one anxiety condition, while nine (11.1%) had a depressive disorder present. Active IBD status was associated with higher prevalence rates across all anxiety and depressive conditions. Generalized anxiety was the most common (12 participants, 14.8%) anxiety condition, and major depressive disorder (recurrent) was the most common depressive condition reported (five participants, 6.2%). Seventeen participants (21%) reported currently seeking help for mental health issues while 12.4% were identified as having at least one psychological condition but not seeking treatment.

Conclusion: We conclude that rates of anxiety and depression are high in this cohort, and that IBD-focused psychological services should be a key component of any holistic IBD service, especially for those identified as having active IBD.

Keywords: inflammatory bowel disease, psychological conditions, disease activity

Introduction

Within the inflammatory bowel disease (IBD) literature, anxiety and depression symptoms are commonly identified to be associated with increased disease activity^{1,2} and reduced quality of life.¹ Research also indicates that ongoing psychological distress can exacerbate disease activity,³⁻⁵ and increase the risk of flare-ups and health care costs.^{4,6,7} Given this, several experts have called for mental health screening and targeted treatment of psychological conditions in IBD cohorts.⁸⁻¹⁰ Despite there being approximately 70,000 Australians with IBD,¹¹ limited research has been conducted to explore the prevalence of anxiety and mood disorders within this cohort.

Rates or severity of depression and anxiety within the IBD literature have most commonly been based upon anxiety and/or depression-specific questionnaires, such as the Hospital Anxiety and Depression Scale (HADS).^{3,8,9,12-18} Within IBD cohorts, based on having at least one subscale over 8 (indicating probable diagnosis of anxiety or depression), Guthrie et al⁹ identified a rate of 47.4% in 116 consecutive individuals,

while Bennebroek Evertsz et al⁸ reported a rate of 43% of 231 adult IBD patients. Using the HADS, Andrews et al¹⁹ found 66% of active IBD patients versus (vs) 37% of non-active IBD group had probable anxiety or depression, while Bennebroek Evertsz et al⁸ found that 41.9% with active IBD had scores indicative of depression vs 21.1% with non-active IBD.

While reports of anxiety and depression symptom severity using questionnaires (eg, HADS)²⁰ are quite common in the IBD literature, limited research has been undertaken to identify the prevalence of anxiety and mood disorders within IBD cohorts.^{19,21–23} Based on interviews using the *Diagnostic and Statistical Manual III* (DSM-III)²⁴ criteria, Helzer et al²¹ found that among 50 ulcerative colitis (UC) patients, 26% had a diagnosable condition, with depression being the most common (10%). Andrews et al¹⁹ interviewed 80 IBD patients and found that 27% and 26% of Crohn's disease (CD) and UC patients, respectively, had generalized anxiety disorder (GAD), major depressive disorder (MDD), or dysthymia. Walker et al²² reported that of 40 IBD patients interviewed, lifetime vs current depression were 25% and 3%; panic disorder (PD) lifetime vs current was 25% vs 3%; and 35% had GAD while 15% had obsessive compulsive disorder (OCD).

Using the composite international diagnostic interview^{25,26} with DSM-IV-TR criteria,²⁷ Walker et al²³ found that of 351 IBD patients, 22.2% had at least one mood or anxiety condition at 12 months, while 45.3% had a lifetime prevalence of at least one anxiety or mood condition. Due to the resource-intensive nature of standardized clinical interviews, Fuller-Thomson and Sulman²⁸ reported rates of anxiety and/or depression based upon standardized clinical interview questions in a self-report questionnaire format. Based on two large Canadian IBD cohorts (n=3,076 [2000–2001]) and n=1,438 [1996–1997]), Fuller-Thomson and Sulman reported that 16.3% and 14.7% of responders, respectively, met criteria for depression (based on DSM-III criteria).

To date, of the studies conducted in Australia, rates of depression and anxiety in IBD cohorts have been limited to interpretation from symptom-based questionnaire scales (eg, HADS).^{10,13} For example, Knowles et al¹⁰ reported that based on a sample of 96 patients with Crohn's disease (46% active disease), 44% met the criteria for depression and 65% met the criteria for anxiety. To the authors' knowledge, there are no published data on the prevalence rates of anxiety and depressive disorders or rates of engagement with mental health services in an Australian IBD outpatient cohort. Therefore, the aims of this study were to characterize prevalence rates of anxiety and depressive conditions

and uptake of mental health services in an Australian IBD outpatient setting.

Materials and methods

Patients

Eighty-one adults (39 males, 42 females; 56 with Crohn's disease) from the IBD clinic in one teaching hospital were studied (45% questionnaire return rate). The average age was 35.07 years (standard deviation [SD]=12.51). As identified 55.6% was married or living together with a partner, 43% was single, and 2% did not identify relationship status (Table 1). Patients' mean disease duration was 13.46 years (SD=6.35), 65% had active disease (as defined by the Manitoba Index [MI]), and three patients reported having a stoma. Ethical approval to conduct this research was attained from the St Vincent's Hospital (Melbourne) and Swinburne University of Technology Human Ethics Research Committees.

Disease assessment and questionnaires

MI

The MI²⁹ is a single item assessment of IBD disease activity. Individuals are asked "In the past 6 months my disease has been: a) constantly active, giving me symptoms every day, b) often active, giving me symptoms most days; c) sometimes active, giving me symptoms on some days (for instance 1–2 days/week); d) occasionally active, giving me symptoms 1–2 days/month; e) rarely active, giving me symptoms on a few days in the past 6 months; f) I was well in the past 6 months, what I consider a remission or absence of symptoms." The MI has been found to have excellent sensitivity when compared to standard CD (Harvey-Bradshaw Index) and UC (Powell-Tucker Index) disease activity measures and test-retest reliability.²⁹

HADS

The HADS²⁰ is a 14-item self-report questionnaire assessing levels of anxiety (seven items) and depression (seven items) over the past week. Each question is assessed on a 4-point Likert Scale: "I feel tense or 'wound up'" (0= not at all 3= most of the time). Consistent with recommendations by Bjelland et al³⁰ and research conducted by the authors previously,¹⁰ a cut-off of 8 for each HADS subscale will be used to differentiate normal from mild to severe distress.

The Mini-International Neuropsychiatric Interview (MINI; Version 6.0.0)

The Mini-International Neuropsychiatric Interview (MINI)³¹ is a structured clinical interview used to diagnose psychiatric

Table 1 Sociodemographic and clinical participant characteristics

Characteristics	N	%
Sex		
Male	39	48.1
Female	42	51.9
Location born		
Australia	61	75.1
New Zealand	2	2.5
Europe (UK)	8	9.8
Europe (other)	3	3.7
Asia	2	2.4
Middle East	3	3.7
South Africa	1	1.2
Not identified	1	1.2
Highest education		
Primary school	1	1.2
Secondary school	34	42
Certificate/diploma	22	27.1
Undergraduate degree	18	22.2
Postgraduate degree	5	6.2
Not identified	1	1.2
Relationship status		
Married or with partner	45	55.6
Single	35	43.5
Not identified	1	1.2
Have children		
Yes	32	39.5
No	49	60.5
Employment status		
Full-time	32	39.5
Part-time	8	9.9
Casual	7	8.6
Retired	2	2.5
Home duties	4	4.9
Student	9	11.1
Unemployed	10	12.3
Other	9	11.1
Disease type		
CD	56	69.1
UC	25	30.9
Stoma		
Yes	3	3.7
No	78	96.3
Medications		
Aminosalicylates	32	39.5
Antibiotics	3	3.7
Corticosteroids	15	18.5
Immunomodulators	23	28.4
Biologic	27	33.3
Not reported	11	13.6

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis.

disorders according to DSM-IV-TR²⁷ criteria. Although mostly used by clinicians in an interview format, some researchers have utilized the MINI in questionnaires in a self-report format.³² For the purpose of this study, the MINI was modified with clinician directed prompts being removed. Prior to its use, feedback was attained from experts of mental health

to ensure these modifications were appropriate and allowed participants to self-complete the MINI. Participants were asked to complete all questions relating to MDD (current and recurrent), PD, social anxiety disorder (SAD), and GAD.

Procedures

Patients attending an IBD outpatient clinic were invited to participate in the study, and where possible, missing data were attained from medical records. Inclusion criteria were: patients under the care of the hospital IBD outpatient service and having been diagnosed with IBD, aged over 18 years, and able to read and complete the questionnaire. The recruitment period was from July 25, 2011 to July 3, 2012.

Consistent with previous publications by the Manitoba group,^{33–36} active IBD activity was defined as reporting symptoms on the MI from “constantly” (a) to “occasionally” (d), and inactive (remission) disease activity “rarely” (e) and “well in the last 6 months” (f). Prevalence of psychological disorders was evaluated by MINI in a self-report format.

Results

Sensitivity of MINI diagnosis across HADS subscale scores

As identified in Table 2, 84.2% of patients with an anxiety score equal to or over 8 on the HADS scale (indicating mild to severe distress) were identified with having an anxiety condition according to the MINI scale, while 30.6% of patients with an anxiety score equal to or over 8 were categorized as not having an anxiety condition. In relation to a diagnosis of depression, 42.9% had a depression score equal to or over 8, while 15% of those not diagnosed with depression had a

Table 2 Sensitivity of MINI diagnosis across HADS subscale scores

MINI diagnosis	HADS-anxiety		
	<7	8–10	>11
MINI diagnosis–anxiety			
Yes, n (%)	3 (15.8)	5 (26.3)	11 (57.9)
No, n (%)	43 (69.4)	11 (17.7)	8 (12.9)
	HADS-depression		
	<7	8–10	>11
MINI diagnosis–depression			
Yes, n (%)	12 (57.1)	1 (4.8)	8 (38.1)
No, n (%)	51 (85.0)	6 (10.0)	3 (5.0)

Abbreviations: MINI, Mini-International Neuropsychiatric Interview; HADS, Hospital Anxiety and Depression Scale.

depression score equal to or over 8. Given that 15.8% and 57.1% of anxiety and depression conditions, respectively, were identified by the HADS subscale as a non-case while identified as a case based on the MINI, for the remainder of the results, identification of psychological diagnosis will be based on 1) MINI criteria only and 2) MINI criteria as well as having the relevant HADS subscale score equal to or over 8.

Differences in disease activity, anxiety, and depression scores

As identified in Table 3, there were no significant differences between UC and CD across Manitoba disease severity, and anxiety and depression scores. Females were found to have significantly higher scores for depression and anxiety. No significant differences were found between those with or without a stoma. Active disease status was associated with significantly higher scores across all the disease severity measures and higher rates of depression and anxiety. Higher Manitoba disease severity, anxiety, and depression scores

Table 3 Mean and standard deviations of study variables by IBD type, IBD status, sex, presence of stoma, presence of depressive or anxiety disorder, and if currently seeking treatment

Conditions	MI		HADS-D		HADS-A	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Total sample	81	4.16 (1.55)	81	5.08 (4.44)	81	6.95 (4.60)
IBD type						
CD	56	4.16 (1.46)	56	5.35 (4.90)	56	7.21 (4.75)
UC	25	4.16 (1.75)	25	4.46 (3.20)	25	6.37 (4.26)
P-value		>0.05		>0.05		>0.05
IBD status						
Active	65	4.79 (.96)	65	5.75 (4.55)	65	7.58 (4.67)
Remission	16	1.62 (.50)	16	2.34 (2.62)	16	4.39 (3.27)
P-value		<0.001		<0.01		<0.05
Mood disorder present ^a						
Yes	9	5.33 (.71)	9	13.33 (2.24)	9	13.33 (3.61)
No	72	4.03 (1.58)	71	4.05 (3.46)	72	6.16 (4.07)
P-value		<0.05		<0.001		<0.001
Anxiety disorder present ^a						
Yes	16	4.94 (.93)	16	8.19 (4.81)	16	12.75 (3.04)
No	65	3.97 (1.61)	65	4.31 (4.03)	65	5.53 (3.71)
P-value		<0.05		<0.001		<0.001
Currently seeking treatment						
Yes	17	4.65 (1.32)	17	9.29 (5.06)	17	9.29 (5.06)
No	64	4.03 (1.58)	64	6.33 (4.29)	64	6.33 (4.29)
P-value		>0.05		<0.01		<0.05

Note: ^aBased on participants meeting MINI DSM criteria and the associated HADS subscale score >8.

Abbreviations: IBD, inflammatory bowel disease; MI, Manitoba Index; MINI, Mini-International Neuropsychiatric Interview; DSM, *Diagnostic and Statistical Manual*; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS-anxiety subscale; HADS-D, HADS-depression subscale; SD, standard deviation; UC, ulcerative colitis; CD, Crohn's disease.

were found among those patients identified as having a mood or anxiety disorder. No significant differences were found on Manitoba disease severity between patients seeking mental health support and those not seeking mental health support.

Prevalence of having at least one anxiety or depressive disorder

Out of 81 patients, 31 (38.3%) were identified as having either an anxiety and/or depressive disorder based on MINI criteria; however, when considering only those meeting MINI criteria and the relevant HADS subscale score over 8, 19 (23.5%) participants were identified as having either an anxiety and/or depressive disorder.

Prevalence of anxiety disorders

As shown in Table 4, 23.5% of participants were found to have an anxiety condition, with generalized anxiety being the most common (14.8%). Based on the stricter criteria (MINI and HADS-anxiety subscale) 16 (19.8%) participants were identified as having an anxiety disorder, with GAD being the most frequent (n=12; 14.8%) and PD (current) being the least frequent (n=1; 1.2%). Of the 16 patients identified to be in remission, only two participants (12.5% of patients in remission) were found to have an anxiety condition, one had GAD while the other had OCD. Active disease activity was associated with higher occurrence rates across all anxiety conditions. Based upon stricter criteria, GAD was the most frequent (n=11; 16.9% of disease active patients), while PD (current) was the least frequent anxiety condition (n=1; 1.2% of disease active patients).

Of the 64 patients who noted not currently seeking help for a mental health issue, eight patients (12.5%) were identified as having at least one anxiety disorder with GAD being the most common (n=7, 10.9%). Eight out of 17 patients who reported currently seeking help for a mental health condition were found to have an anxiety condition, with GAD being the most frequent (n=5, 29.4%) and SAD and OCD conditions were each found in three patients (17.6%). PD (current) was the least frequent anxiety condition in the cohort seeking help for mental health (n=1, 1.5%).

Prevalence of depressive disorders

As shown in Table 5, 25.9% of participants were found to have a depressive condition, with dysthymia being the most common (9.9%). Based on the stricter criteria (MINI and HADS-depression subscale) nine (11.1%) participants were

Table 4 Distribution of anxiety conditions by total sample, IBD status, and currently seeking treatment

Conditions	Total sample		Total sample ^a		IBD status ^a				Currently seeking treatment ^a			
	N	%	N	%	N	Active	N	Remission	N	Yes	N	No
Panic disorder												
Yes	3	3.7%	3	3.7%	3	4.6%	0	0%	3	17.6%	0	0%
No	78	96.3%	78	96.3%	62	95.4%	16	100%	14	82.4%	64	100%
Panic disorder (current)												
Yes	1	1.2%	1	1.2%	1	1.5%	0	0%	1	5.9%	0	0%
No	80	98.8%	80	98.8%	64	98.5%	16	100%	16	94.1%	64	100%
Panic disorder (lifetime)												
Yes	2	2.5%	2	2.5%	2	3.1%	0	0%	2	11.8%	0	0%
No	79	97.5%	79	97.5%	63	96.9%	16	100%	15	88.2%	64	100%
Social anxiety disorder												
Yes	6	7.4%	6	7.4%	6	9.2%	0	0%	3	17.6%	3	4.7%
No	75	92.6%	75	92.6%	59	90.8%	16	100%	14	82.4%	61	95.3%
Generalized anxiety disorder												
Yes	12	14.8%	9	11.1%	11	16.9%	0	0%	5	29.4%	7	10.9%
No	69	85.2%	72	88.9%	54	83.1%	16	100%	12	70.6%	57	85.2%
Obsessive compulsive disorder												
Yes	6	7.4%	5	6.2%	5	7.7%	0	0%	3	17.6%	3	4.7%
No	75	92.6%	76	93.8%	60	92.3%	16	100%	14	82.4%	61	95.3%
Post-traumatic stress disorder												
Yes	3	3.7%	3	3.7%	3	4.6%	0	0%	2	11.8%	1	1.6%
No	78	96.3%	78	96.3%	62	95.4%	16	100%	15	88.2%	63	98.4%
Anxiety disorder present												
Yes	19	23.5%	16	19.8%	16	24.6%	0	0%	8	47.1%	8	12.5%
No	62	74.1%	65	80.2%	49	75.4%	16	100%	9	52.9%	56	87.5%

Note: ^aBased on participants meeting MINI DSM criteria and a HADS-anxiety subscale score >8.

Abbreviations: IBD, inflammatory bowel disease; MINI, Mini-International Neuropsychiatric Interview; DSM, *Diagnostic and Statistical Manual*; HADS, Hospital Anxiety and Depression Scale.

identified as having a depressive disorder, eight (9.9%) had MDD (n=3 had major depressive episode [current]; n=5 had major depressive episode [recurrent]). One patient (1.2%) had dysthymia. None of the 17 patients in remission had a depressive condition. Active disease activity was associated

with higher occurrence rates across all depressive conditions. Major depressive episode (recurrent) was the most frequent (n=5; 7.7% of disease active patients), while dysthymia (current) was the least frequent depressive condition (n=1; 1.5% of disease active patients).

Table 5 Distribution of depressive conditions by total sample, IBD status, and currently seeking treatment

Conditions	Total sample		Total sample ^a		IBD status ^a				Currently seeking treatment ^a			
	N	%	N	%	N	Active	N	Remission	N	Yes	N	No
Major depressive episode												
Yes	13	16.0%	8	9.9	8	12.3%	0	0%	5	29.4%	3	4.7%
No	68	84.0%	73	90.1	57	87.7%	16	100%	12	70.6%	61	95.3%
Major depressive episode (current)												
Yes	6	7.4%	3	3.7	3	4.6%	0	0%	3	17.6%	0	0%
No	75	92.6%	78	96.3	62	95.4%	16	100%	14	82.4%	64	100%
Major depressive episode (recurrent)												
Yes	7	8.6%	5	6.2	5	7.7%	0	0%	2	11.8%	3	4.7%
No	74	91.4%	76	93.8	60	92.3%	16	100%	15	88.2%	61	95.3%
Dysthymia												
Yes	8	9.9%	1	1.2	1	1.5%	0	0%	0	0%	1	1.6%
No	73	90.1%	80	98.8	64	98.5%	16	100%	17	100%	63	98.4%
Depressive disorder present												
Yes	21	25.9%	9	11.1	9	13.8%	0	0%	5	29.4%	4	6.3%
No	60	74.1%	72	88.9	56	86.2%	16	100%	12	70.6%	60	93.8%

Note: ^aBased on participants meeting MINI DSM criteria and a HADS-depression subscale score >8.

Abbreviations: IBD, inflammatory bowel disease; MINI, Mini-International Neuropsychiatric Interview; DSM, *Diagnostic and Statistical Manual*; HADS, Hospital Anxiety and Depression Scale.

Patients currently seeking mental health support

Of the 81 patients, 17 reported seeking help for a current mental health issue, seven (41.2%) were male. The average length of time reported seeing their mental health expert was 33.21 months (SD =81.77), with the range being 1 month to 26 years. Five out of 17 (29.4%) patients who reported currently seeking help for a mental health condition were found to have a depressive condition with major depressive episode (current) being the most frequent (n=3, 17.6%). Of the 64 patients who noted not currently seeking help for a mental health issue, ten participants (12.4%) were identified as having at least one psychological condition. Of the ten participants, four (12.5%) patients were identified as having a depressive disorder (three patients had MDD-recurrent, one patient had dysthymia), five met criteria for GAD, three met criteria for SAD, two met criteria for OCD, one met criteria for post-traumatic stress disorder, four met criteria for MDD, and one met criteria for dysthymia.

Medication use

Fifteen out of 81 (18.5%) patients reported taking psychotropic medications, with ten (66.7%) currently seeking mental health support. The average length of time reported being on psychotropic medication was 37.2 months (SD =39.59), with the range being 3 weeks to 9 years.

Discussion

To the authors' knowledge, this is the first study to explore the prevalence of anxiety and depressive conditions in an Australian outpatient cohort. Further, we explored the rates of mental-health help seeking behavior. The finding that 19.8% and 11.1% of our sample met criteria on the stricter definition for an anxiety or mood disorder, respectively, is consistent with two population-based studies (USA:³⁷ 18.1% and 9.5%; New Zealand:³⁸ 14.8% and 8%). Our result indicating that 23.5% had at least one anxiety or depressive disorder is consistent with prevalence rate of 22.2% and 26.0% reported by Walker et al²³ and Helzer et al,²¹ respectively. In comparison to Walker et al, our prevalence rates were also similar across depressive disorders (MDD: 9.1% vs 9.9%; dysthymia: 0.6% vs 1.2%) and anxiety disorders (PD: 3.7% vs 3.7%; post-traumatic stress disorder: 4.0% vs 3.7%). However, it should be noted that our study tended to have higher rates of GAD, SAD, and OCD compared to the Walker et al's study (GAD: 11.1% vs 3.7%; SAD: 7.4% vs 2.6%; OCD: 6.2% vs 1.0%).

Our findings in relation to HADS scores over 8 (ie, 43% having anxiety, 22% having depression) is consistent with the

previous Australian-based HADS studies, who have reported a range of 11%–44% for anxiety and from 37%–65% for depression.^{10,13,39} Consistent with previous research,^{8,19,40} active IBD status is associated with higher prevalence rates across all anxiety and depressive conditions and significantly higher scores on the anxiety and depression subscales.

In terms of seeking mental health services, 21.0% of participants reported seeking help for a current mental health issue, while 12.4% were identified as having at least one psychological condition but not seeking treatment. Fifteen out of 81 (18.5%) patients reported taking psychotropic medications and of these 15, ten participants reported currently seeking mental health support. These findings suggest that while the majority of individuals with a mental health condition seek treatment, a minority do not. Further, even those who do have support, continue to report criteria meeting a psychological condition. This may suggest that while individuals are attaining support, more is needed.

Limitations and future studies

While our findings are consistent with other IBD prevalence-based studies, a major limitation of this study was the use of self-reported data to identify diagnosis rather than standardized interviews. However, we sought to validate diagnosis by ensuring that it was also associated with a probable diagnosis using a validated frequently used scale (HADS) and combined with the MINI which has been used previously in self-report format.³² We also note that only 45% of the questionnaires were returned, so the results will only reflect these patients and not the entire hospital IBD cohort. It must also be noted that the cohort investigated in this study was cross-sectional, English speaking, and relatively small, especially remission sub-group (n=16). Future studies could address these limitations by undertaking a consecutive IBD sample matched to a general population cohort. A final limitation was the utilization of the MI. While the index is well validated, it provides a perceived measure of disease activity not one based on clinical criteria. Future research could also consider exploring the links between psychological conditions within IBD cohorts and their potential links to stress, illness perceptions, personality, social support and attachment patterns, and coping styles.^{10,15,34,41,42}

Conclusion

To the authors' knowledge, our study is the first to identify the rates of depression and anxiety disorders in an Australian IBD outpatient setting. Our results are consistent with those found in IBD interview-based prevalence studies conducted

in Canada and USA.^{21,23,28} It is also clear that active IBD is associated with higher rates of anxiety and depression disorders also consistent with symptom-based studies conducted to date.^{17,19} Our results also provide evidence that while many patients with IBD and a psychological disorder seek support, that support may not be sufficient. Further, although based on a small sample size, approximately 12% of our cohort met criteria for a mental health condition, but were not seeking treatment for it. These findings provide further evidence for the need of psychological services to be part of any IBD service. As a practical starting point, IBD patients, especially patients with active disease, should be screened for psychological distress.

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Author contributions

All authors contributed equally to the conception and design of the study, data collection, and critical revision of the manuscript, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that there are no conflict of interests regarding the publication of this paper.

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