

Examining the Complex Interplay of Pain Perception, Pain Anxiety, and Mental Health problems in Thalassemia Patients: A Mediation Analysis

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Abstract

Background: Thalassemia is a heterogeneous genetic disorder globally that stems from diminished synthesis of alpha and beta chains of hemoglobin and results in accelerated destruction of red blood cells. This condition is linked to different mental health problems, including pain perception, mood, depression, and anxiety disorders, with pain being a predominant symptom. The present study aims to investigate the complex association among pain perception, perception of pain anxiety, depression disorder, anxiety disorder, and positive and negative affect in thalassemia patients. Moreover, it seeks to elucidate the possible mediating role of pain anxiety perception in the relationship between pain perception and depression disorder, anxiety disorder, and affective states in thalassemia patients.

Method: A purposive sampling technique and cross-sectional design were used in the present study. One hundred diagnosed thalassemia patients (males, $n = 56$, females, $n = 44$) whose ages ranged from 12 to 18 years were recruited from the thalassemia departments of the Jamila Sultana Foundation, the Federal Government Polyclinic (FGPC), and the Pakistan Thalassemia Welfare Society located in Rawalpindi and Islamabad in Pakistan from October 1, 2023, to January 1, 2024. Five standardized psychological instruments were employed to examine pain perception, pain anxiety, depression disorder, anxiety disorder, and positive and negative affect in thalassemia patients.

Results: The study's findings found that pain perception is significantly associated with pain anxiety, negative affect, depression, and anxiety disorders in thalassemia patients, while it is negatively correlated with positive affect. Gender differences exhibited that males display higher levels of negative affect as compared to females, with no significant differences in perceptions of pain anxiety, pain perception, positive affect, depression, or anxiety disorder. Moreover, pain anxiety acts as a mediator in the relationship between pain perception and depression disorder in patients with thalassemia.

Conclusions: This study suggests that the interplay between pain perception and pain anxiety significantly contributes to mental health problems in Pakistani thalassemia patients, specifically depression disorder. It highlights the importance of tailored psychosocial interventions developed collaboratively by researchers, healthcare providers, and mental health professionals to address mental health challenges and improve the overall quality of life for individuals with thalassemia.

Keywords: Pain perception, pain anxiety, depression disorder, anxiety disorder, and positive and negative affect, thalassemia patients.

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Background

Thalassemia poses a substantial global health burden that requires enduring medical care and management plans to alleviate its influence on affected persons' quality of life (Albahout et al., 2023; Drahos et al., 2024; Galanello & Origa, 2010; Jamil et al., 2024; Palanisamy et al., 2024; Patel et al., 2019; Rehman et al., 2023; Sarhan et al., 2022; Yousuf et al., 2022; Yusoff et al., 2013). It poses an important global health problem, affecting 72% of the 229 nations globally. Around 5.2% of the international populace, 1% of couples, and 7% of pregnant women are at risk of thalassemia. According to a report by the World Health Organisation (WHO), carriers constitute 5% of the global population, and alarmingly, about 17% of newborns each year transmit the thalassemia genetic factor (Tarım & Öz, 2022). It comprises a diverse range of congenital disorders rising from diminished synthesis of the alpha and beta chains of haemoglobin, which is very crucial for oxygen transportation in red blood cells (Jamil et al., 2024; Khaliq, 2022; Palanisamy et al., 2024; Patel et al., 2019).

This chronic blood disease is normally inherited and manifests as anemia between early childhood and adulthood. It is mainly triggered through genetic mutations or the removal of vital gene fragments (Black et al., 2024; Drahos et al., 2024). Alpha-thalassemia effects from alpha-globin gene removals, which further differ in severity based on allele removals. On the other hand, β -thalassemia is the result of point mutations in the beta-globin gene, which leads to forms such as Thalassemia Major, which is known as Cooley's anemia. β -thalassemia poses health risks because of reduced beta-protein formation, which leads to life-threatening anemia and requires consistent blood transfusions as well as chelation treatment to control iron overload or stop organ failure (Albahout et al., 2023; Black et al., 2024; Khaliq, 2022; Palanisamy et al., 2024; Yousuf et al., 2022).

B-thalassemia, an inherited hemoglobinopathy, is clinically diagnosed in around 40,000 newborns globally every year. Of these, 25,500 of them have transfusion-dependent β -thalassemia (Angastiniotis, 2024; Drahos et al., 2024; Economidou et al., 2024; Modell & Darlison, 2008; Shah et al., 2019). In Pakistan, the prevalence of the β -thalassemia trait ranges from 5.0% to 7.0%, resulting in more than 10 million carriers throughout the country. Moreover, roughly 5000 offspring are clinically diagnosed yearly with carrying β -thalassemia major (Asif et al., 2016; Khaliq, 2022). In β -thalassemia, mutations in the β -globin gene result in the absence or diminished production of β -chains in children's haemoglobin, which leads to ineffective chronic anemia and erythropoiesis (Angastiniotis, 2024; Aqeel et al., 2017; Galanello & Origa, 2010; Khan & Aqeel, 2022; Peters & Aqeel, 2020). B-Thalassemia is also an advanced condition linked to the onset of different clinical problems affecting the skeletal, endocrine, cardiovascular, and hepatic systems and psychological problems including pain, anxiety, mood problems, and depression in affected individuals (Aqeel et al., 2022; Fatima et al., 2022; Taher et al., 2018; Tarım & Öz, 2022).

Furthermore, thalassemia foremost represents a noteworthy mental health problem for patients, which is impacting numerous aspects of their lives, such as physical and mental health, independence, personal beliefs, social relationships, and overall quality of life (Abbasi & Aqeel,

2023; Aqeel et al., 2018, 2020, 2021; Aqeel & Ahmed, 2018; Hood et al., 2024; Jamil et al., 2024; Munawar et al., 2021; Shuja et al., 2022; Tariq et al., 2023). The chronic nature of thalassemia, which requires lifelong regular transfusions and tertiary care, is associated with challenges that contribute to hopelessness, anxiety, depression, and mood problems in affected patients (Abida et al., 2023; Aqeel et al., 2021, 2022; Aziz et al., 2012; Chaman et al., 2022; Hood et al., 2024; Jamil et al., 2024; Rehman et al., 2023; Shuja et al., 2021; Shuja et al., 2020; Siddiqui et al., 2014; Tarım & Öz, 2022).

Although the worldwide prevalence of thalassemia and its severe psychological effects are known, studies on mental health problems in thalassemia patients remain unclear, outdated, and further open for debate, especially in the Pakistani context (Jamil et al., 2024; Siddiqui et al., 2014). Previous research lacks detailed knowledge on mental health issues and their consequences and fails to address the association and interplay among perceived pain, pain anxiety, and psychological distress in Pakistani thalassemia patients (Abbasi & Aqeel, 2023; Aziz et al., 2012; Bhatti et al., 2023; Gul et al., 2022; Jamil et al., 2024; Khattak, 2023; Naeem et al., 2021; Noor et al., 2016; Rehman et al., 2023; Shuja, Aqeel, et al., 2020; Siddiqui et al., 2014). Therefore, there is a dire need for advanced study in this field to better comprehend and manage the mental health challenges faced by thalassemia patients. This study contributed to the previous literature by examining the prevalence of psychiatric issues including pain perception, pain anxiety, depression, and positive and negative mood swings in thalassemia patients.

Moreover, this study aimed to examine the relationship between perception of pain anxiety, perception of pain intensity, depression, and anxiety disorders in patients with thalassemia. Additionally, this study seeks to elucidate the possible mediating role of perception of pain anxiety in the relationship between the perception of pain and depression. Furthermore, it endeavors to examine gender-based differences in the perception of pain anxiety, depression, and anxiety disorders across male and female thalassemia patients. This study aimed to contribute to a deeper insight into the prevalence of psychosocial aspects of thalassemia management, thus also guiding more effective interventions as well as support strategies for affected Pakistani thalassemia patients. This study was also providing valuable deep insights to guide comprehensive care and support plans for this vulnerable population.

Method

Objectives and hypotheses

The present study aimed to investigate the complex relationship among pain perception, perception of pain anxiety, depression disorder, anxiety disorder, and positive and negative affect in thalassemia patients. Furthermore, it sought to reveal the possible mediating role of perception of pain anxiety in the relationship among pain perception, depression disorder, anxiety disorder, and positive and negative affect in thalassemia patients. Additionally, it was designed to examine gender-based differences in pain and anxiety perception, depression disorder, anxiety disorder, and positive and negative affect in male and female thalassemia patients.

Research design and sample

A purposive sampling technique and cross-sectional design were used in the present study. One hundred diagnosed thalassemia patients (males, $n = 56$, females, $n = 44$) whose ages ranged from 12 to 18 years were recruited from the thalassemia departments of the Jamila Sultana Foundation, the Federal Government Polyclinic (FGPC), and the Pakistan Thalassemia Welfare Society located in Rawalpindi and Islamabad in Pakistan from October 1, 2023, to January 1, 2024. Approval for this study was obtained from the Ethical Review Board of the Department of Psychology, the School of Science and Technology, Pakistan. Verbal and written informed consent were obtained from all volunteer participants prior to their involvement in the study. Further inclusion criteria included patients diagnosed with β -thalassemia major who were included in the present study. Exclusion criteria were set to exclude participants who had undergone hematopoietic stem cell transplants at any time in their medical history. Moreover, exclusion criteria encompassed patients with any history of psychiatric disorders and severe cognitive impairment that could impede their cognitive ability to provide informed consent or appropriately contribute to the study's examinations.

Measures

Five standardized instruments, including the Beck Depression Inventory, Beck Anxiety Inventory, Pain Anxiety Symptom Scale, Pain Perception Scale, and Positive and Negative Affect Schedule, were utilized to examine depression disorder, anxiety disorder, pain perception, pain anxiety, and positive and negative affect in thalassemia patients.

Pain anxiety symptoms scale

The Pain Anxiety Symptoms Scale (PASS; Cracken, 1992) is employed to assess fear and anxiety responses specific to pain (McCracken et al., 1992; Shuja et al., 2021). It encompasses 20 items that are designed to examine anxiety levels practiced in pain episodes. It was translated into Urdu language in medical patients (Shuja et al., 2021). It has four subscales: fear (4 items), cognitive (6 items), and physiological anxiety (5 items), and escape avoidance (5 items). Participants provide ratings on a six-point scale that ranges from 0 (never) to 5 (always). The subscales of the scale comprise cognitive (items 1 to 5), physiological anxiety (items 16 to 20), escape or avoidance (items 6 to 10), and fear (items 11 to 15). This study has shown high reliability and validity for the present sample.

The Beck Depression Inventory (BDI)

The BDI is a self-reporting instrument designed to measure the severity of depression in the psychiatric population (Beck et al., 1961, 1996). It consists of 21 items, with scores measured on a four-point Likert scale ranging from 0 (absence of symptoms) to 3 (severe symptoms). For patients diagnosed with depression, scores from 0 to 13 show minimal depression, 14–19 reveal mild depression, 20–28 display moderate depression, and 29–63 indicate severe depression (Beck et al., 1996). The scale ranges from a minimum score of 0 to a maximum score of 63. Additionally, the Cronback alpha reliability of the present study was satisfactory for the current population.

The Beck Anxiety Inventory (BAI)

The Beck Anxiety Inventory (BAI) is a self-reporting

instrument designed to examine anxiety severity in clinical people and healthy populations (Beck et al., 1993; Fydrich et al., 1992; Starosta & Brenner, 2018; Steer & Beck, 1997). It consists of 21 items, and each item's score is measured on a Likert scale based on four points ranging from 0 (not at all) to 3 (severity—it bothered me a lot). In those diagnosed with anxiety, scores of 0–7 indicate low or minimal anxiety, 8–15 show mild anxiety, 16–25 show moderate anxiety, and scores of 26–63 show severe anxiety among people (Beck et al., 1993; Fydrich et al., 1992; Starosta & Brenner, 2018; Steer & Beck, 1997). Moreover, the Cronback alpha reliability of the present study was satisfactory for the current population.

Positive and Negative affect schedule scale (PANAS)

PANAS is developed to measure positive and negative effects in clinical and normal populations (Tellegen et al., 1999). It comprises a 10-item scale and is further comprised of two domains: positive affect (items 1, 3, 5, 9, 10) and negative affect (items 2, 4, 6, 7, 8). Each item's score is measured on a Likert scale based on five points ranging from (1) very slightly or not at all, (2) a little, (3) moderately, (4) quite a bit, and (5) extremely (Tellegen et al., 1999). This study has shown high reliability and validity for the present sample.

The Wong-Baker pain scale (WBS)

WBS was developed to measure a different level of pain intensity in clinical and normal populations. It consists of six faces, each demonstrating a level of pain intensity (Garra et al., 2010, 2013). The scale gives a numeric value to each face, with higher numbers representing higher pain intensity. Especially, the first face links to a pain score of 0, which demonstrates "no pain intensity." Afterward, the second face embodies a pain score of 2, demonstrating "mild pain intensity." The third face matches a pain score of 4, representative of "moderate pain intensity." The fourth face characterizes a pain score of 6, demonstrating "severe pain intensity." The fifth face links to a pain score of 8, which demonstrates "very or strongly severe pain intensity." Finally, the sixth face denotes a pain score of 10, demonstrating "worst possible pain intensity." Higher scores of scale reflects higher intensity of pain. This study has shown high reliability and validity for the present sample.

Procedure

This study was approved by the ethical review board at the Department of Psychology, the School of Science and Technology, Pakistan, and adhered to the guidelines of the American Psychological Association. One hundred thalassemia patients were incorporated from the thalassemia departments of the Jamila Sultana Foundation, the Federal Government Polyclinic (FGPC), and the Pakistan Thalassemia Welfare Society located in Rawalpindi and Islamabad in Pakistan. Written and verbal informed consent were obtained from all volunteer participants. Permission was obtained from the higher authorities in the thalassemia department and from the participants themselves after providing a comprehensive explanation of the study's aim and ensuring the confidentiality of all data. Prior to completing the scales, volunteer participants were required to sign a written and verbal informed consent form outlining the nature of the study. All volunteer participants were native Urdu speakers and had the ability to write and read. Five standardized instruments, including the Beck Depression Inventory, Beck Anxiety Inventory, Pain Anxiety Symptom

Scale, Pain Perception Scale, and Positive and Negative Affect Schedule, were utilized to examine the prevalence of psychiatric issues and confirm other hypotheses of study in thalassemia patients. Person correlation, the independent sample t-test and mediational analysis were carried out to confirm the objective of the present study (Field, 2013).

Results

In Table 1, this study's results revealed that pain perception is statistically significantly associated with perceptions of pain anxiety, depression, anxiety, and mood disorders. Specifically, pain perception demonstrated a statistically significant positive association with perception of pain anxiety, anxiety disorder, depression disorder, and negative affect, whereas exhibiting a statistically significant negative association with positive affect in thalassemia patients. Similarly, symptoms of anxiety disorder exposed a statistically significant positive relationship with perception of pain anxiety, pain perception, and both positive and negative affect in thalassemia patients. Moreover, perception of pain anxiety was statistically significantly positively linked with pain perception, positive and negative affect.

The independent sample t-test results Table 2 revealed a significant difference in negative affect (NA) ($t = 2.06$, $p > 0.04$) between female ($M = 12.7$, $SD = 2.06$) and male ($M = 14.05$, $SD = 2.98$) patients with thalassemia. Previous studies suggested that female thalassemia patients would exhibit higher negative effects as compared to males, but the results of this study did not support these findings. Moreover, there were non-significant differences in perception of pain anxiety, perception of pain perception, depression disorder, anxiety disorder, and positive affect (PA) between male and female thalassemia patients. These results highlight gender differences in negative affective experiences in Pakistani thalassemia patients and underscore the significance of tailored interventions to comprehend mental health issues, especially negative mood swings, in this population.

In Table 3, the results exhibited that perception of pain was a significant positive predictor predicting ($\beta = 2.91$; $p > .00$) of depression disorders in Pakistani thalassemia patients. Similarly, perception of pain was also significantly predicting ($\beta = 2.91$; $p > .00$) perception of pain anxiety in thalassemia patients. Additionally, the results exhibited that perception of pain anxiety was positively predicting ($\beta = .22$; $p < .00$) depression in thalassemia patients. These results recommend that perception of pain anxiety acts as a partial mediator in the relationship between perception of pain and depression disorder in thalassemia patients. This study's findings build upon past results by explaining the interplay among perception of pain, perception of pain anxiety, and depression disorder in thalassemia patients, which highlights the potential importance of addressing perception of pain anxiety in mental health interventions targeting depression disorder in thalassemia patients.

Discussion

The present study aimed to investigate the complex relationship among pain perception, perception of pain anxiety, depression disorder, anxiety disorder, and positive and negative affect in thalassemia patients. Furthermore, it sought to reveal the possible mediating role of perception of pain anxiety in the relationship among pain perception, depression disorder, anxiety disorder, and positive and

negative affect in thalassemia patients. Additionally, it was designed to examine gender-based differences in pain and anxiety perception, depression disorder, anxiety disorder, and positive and negative affect in male and female thalassemia patients. Through these examinations, this research is designed to offer deeper visions into the prevalence of mental health issues in thalassemia management, therefore enlightening more effective support strategies and interventions to tackle psychological issues within Pakistani thalassemia patients.

This study's results confirm the notion that pain perception is an important symptom in male and female thalassemia patients and closely intertwined with mental health problems including pain anxiety, depression, anxiety, and mood disorders. Specifically, pain perception demonstrated a statistically significant positive association with perception of pain anxiety, anxiety disorder, depression disorder, and negative affect, whereas exhibiting a statistically significant negative association with positive affect in thalassemia patients. Similarly, symptoms of anxiety disorder exposed a statistically significant positive relationship with perception of pain anxiety, pain perception, and both positive and negative affect in thalassemia patients. Moreover, perception of pain anxiety was statistically significantly positively linked with pain perception, positive and negative affect. These findings are aligned with previous investigation that providing additional evidence of the intricate interplay between mental health issues and thalassemia symptoms (Albahout et al., 2023; Drahos et al., 2024; Galanello & Origa, 2010; Jamil et al., 2024; Palanisamy et al., 2024; Patel et al., 2019; Rehman et al., 2023; Sarhan et al., 2022; Yousuf et al., 2022; Yusoff et al., 2013).

Moreover, the present study explored gender differences in pain perception, perception of pain anxiety, anxiety disorder, depression disorder, and positive and negative affect. Interestingly, this study's findings showed that males exhibit higher levels of negative affect as compared to females. However, there were non-significant gender differences in perceptions of pain anxiety, pain perception, depression disorder, anxiety disorder, and positive affect. These results vary from prior studies proposing a higher prevalence of psychological problems in female thalassemia patients (Jamil et al., 2024; Khaliq, 2022; Palanisamy et al., 2024; Patel et al., 2019). These results highlight the importance of considering gender-based differences in the mental health problems of thalassemia patients.

While our investigation elucidated the mediating role of pain anxiety among pain perception, anxiety disorder, depression disorder, and positive and negative affect in patients with thalassemia, The results exhibited that pain anxiety directly or indirectly influences the relationship between pain perception and depression disorder. This study suggested that pain anxiety serves as a mediator in the relationship between pain perception and depression disorder in thalassemia patients (Black et al., 2024; Drahos et al., 2024). This study contributes to a deeper insight into the psychosocial factors of thalassemia management in the Pakistani context.

Results

Table 1

Correlation matrix, alpha cronbach reliability, mean and standard deviation of depression disorder (DEP), anxiety disorder (ANX), perception of pain anxiety (PAN), perception of pain perception (PP), positive and negative affect schedule (PANAS), positive affect (PA), and negative affect (NA) in thalassemia patients (N = 100).

	α	M	SD	1	2	3	4	5	6	7
1. DEP	.949	9.76	10.06	-	.58**	.59**	.56**	.27**	-.06	.52**
2. ANX	.949	11.74	9.05		-	.74**	.52**	.40**	.23*	.39**
3. PAN	.727	33.81	27.17			-	.52**	.19	.03	.26**
4. PP	.737	3.78	1.94				-	.40**	.14	.49**
5. PANAS	.879	26.69	5.33					-	.78**	.68**
6. PA	.835	13.23	3.89						-	.09
7. NA	.698	13.46	3.29							-

*Note: DEP = Depression disorder; ANX = Anxiety disorder; PAN = Perception of pain anxiety; PP = Perception of pain perception; PANAS = Positive and negative affect schedule, PA= Positive affect; NA= Negative affect * $p < .05$, ** $p < .01$, *** $p < .000$*

Table 2

Gender wise mean differences on depression disorder (DEP), anxiety disorder (ANX), perception of pain anxiety (PAN), perception of pain perception (PP), positive and negative affect schedule (PANAS), positive affect (PA), and negative affect (NA) in thalassemia patients (N=100)

Variables	Male (n = 56)		Female (n = 44)		t(df)	p	95% CL		Cohn's d
	M	SD	M	SD			LL	UL	
1. DEP	11.21	10.6	7.97	9.06	1.64	0.1	-0.68	7.29	-
2. ANX	12.01	8.77	11.38	7.71	0.34	0.73	-3	4.26	-
3. PAN	34.25	29.4	33.25	27.2	0.18	0.85	-9.67	11.67	-
4. PP	3.82	1.87	3.72	1.61	0.23	0.81	-0.68	0.87	-
5. PANAS	13.42	3.85	12.97	2.81	0.57	0.56	-1.11	2.01	-
6. PA	14.05	2.98	12.7	2.06	2.06	0.04	0.05	2.64	.52

*Note: DEP = Depression disorder; ANX = Anxiety disorder; PAN = Perception of pain anxiety; PP = Perception of pain perception; PANAS = Positive and negative affect schedule, PA= Positive affect; NA= Negative affect * $p < .05$, ** $p < .01$, *** $p < .000$*

Table 3

The mediating role of perception of pain anxiety between pain perception and depression disorder in patients diagnosed with thalassemia (N=100).

DV	IV	B	SD	β	p
DEP	PP	2.91	.43	.56	.00
	PP	7.30	1.20	.52	.00
	PAN	.22	.03	.59	.00

*Note: DEP = Depression disorder; PAN = Perception of pain anxiety; PP = Perception of pain perception, * $p < .05$, ** $p < .01$, *** $p < .000$*

This study is also shedding light on the intricate association among pain perception, perception of anxiety, and mental health in thalassemia. It also demanded that healthcare and mental health professional's better develop new psychosocial interventions to address the mental health issues of affected thalassemia individuals, ultimately improving their mental well-being and quality of life (Tarim & Öz, 2022).

Limitation and implications

The present study encountered various drawbacks that warrant discussion. Firstly, its cross-sectional research design prohibits causal inferences and limits the generalization of findings in thalassemia, therefore limiting our depth of understanding about causal inferences. Moreover, the small sample size also restricts the generalizability of results to larger thalassemia populations, highlighting the dire need for larger, more different cohorts in upcoming studies. Finally, the study solely concentrated on thalassemia patients aged 12 to 18, possibly overlooking valuable visions from other age groups.

In spite of these restrictions, this study contributes considerably to our understanding of the prevalence of psychological disorders in patients with thalassemia. Furthermore, it highlights gender differences in the prevalence of mental health problems, offering valuable insights for educational and clinical purposes.

Conclusion

This study underscores the potential of pain perception as a catalyst for mental health problems, particularly depression disorder, and mediates the perception of pain anxiety in Pakistani thalassemia patients. The study also significantly improves our understanding of the psychosocial underlying factors inherent in Pakistani thalassemia management. This study was elucidating the intricate interplay among pain perception, perception of pain anxiety, and mental health outcomes in thalassemia patients. This study's findings emphasize the dire need for tailored psychosocial prevention and interventions. These psychosocial interventions should be developed collaboratively by research scholars, healthcare professionals, and mental health professionals to effectively understand and address the mental health challenges faced by people affected by thalassemia. Finally, these

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psychosocial interventions have the potential to significantly enhance the mental health and overall quality of life of Pakistani thalassemia patients.

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Ethical Consideration

The study was approved by Department of Psychology, Foundation University School of Science and Technology, Pakistan. Consent Form was taken before taking data and participants were asked to take voluntary participation.

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Availability of data and materials

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions/Author details

Maham Mushtaq performed this study under the guidelines of American Psychological Association.

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Ethics declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Department of Psychology, Foundation University School of Science and Technology, Pakistan. A written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare to have no competing interests.

Additional Information

Not applicable.

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