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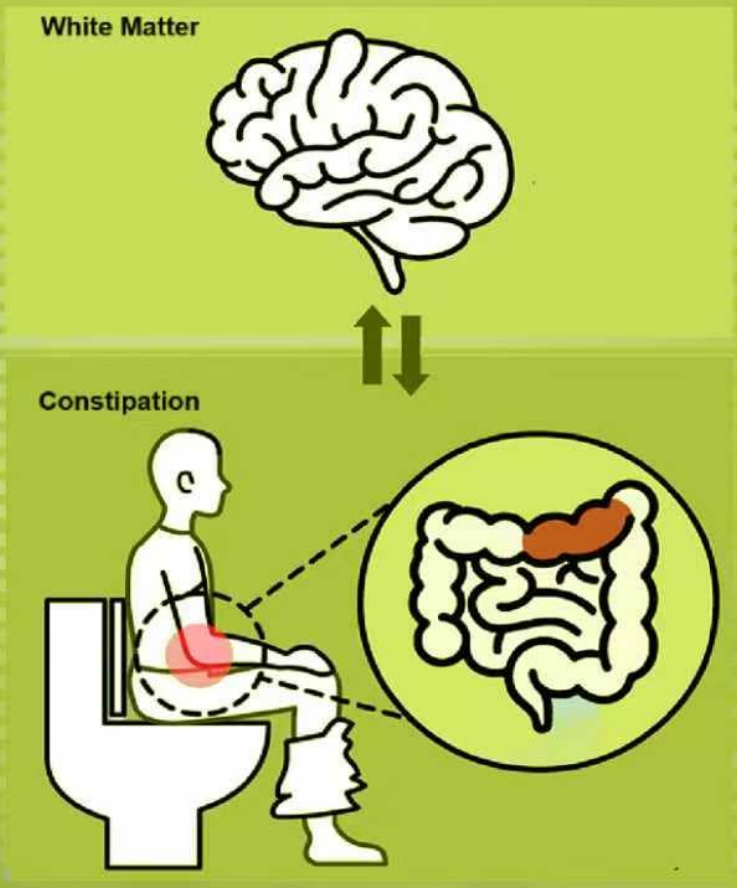

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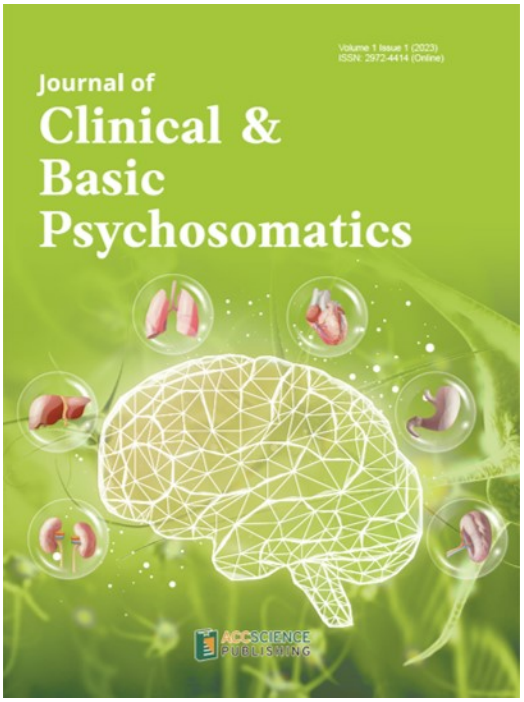

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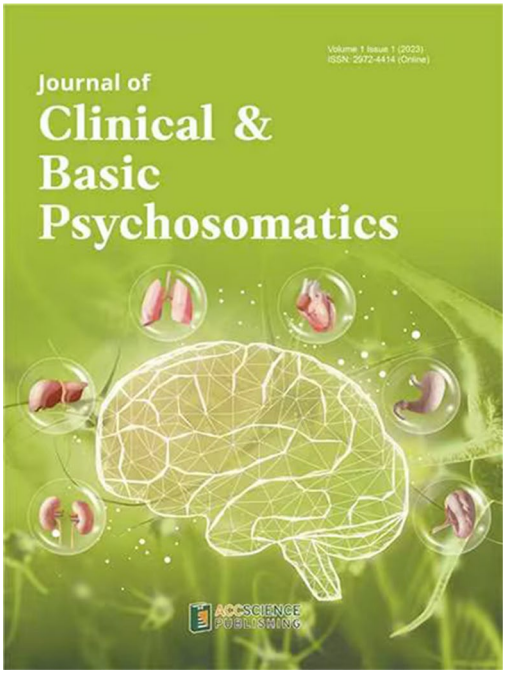

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Volume 4 | Issue 1 | January 2026 | Page 1 – 105 |

Journal of Clinical and Basic Psychosomatics

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CONTENTS

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Journal of Clinical and Basic Psychosomatics

REVIEW ARTICLE

The immune status questionnaire: A critical review

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Abstract

Immune fitness, defined as the adequate functioning of the immune system, is essential for maintaining health, preventing and resolving disease, and improving quality of life. The immune status questionnaire (ISQ) is a self-assessment tool developed to evaluate the type and frequency of seven common immune-related complaints. This review was conducted to provide a comprehensive overview of studies that utilized the ISQ and provide recommendations for its future improvement. A literature search on Google Scholar, supplemented by cross-referencing, identified 91 publications, of which 51 (from 38 independent studies) reported ISQ data and were included in this review. These studies were conducted in 14 countries, with the ISQ translated into six languages. They were cross-sectional and experimental studies involving healthy subjects or patient populations, with sample sizes ranging from 22 to 45,782 participants. Findings revealed that ISQ scores significantly differed across demographics (e.g., sex and age) and health status (e.g., obesity and diabetes). Significant correlations were found between ISQ scores and various health correlates, including positive correlations with lifestyle factors – such as regular physical activity, attaining a daily diet, and adequate sleep – and negative correlations with mood states such as anxiety and depression, alcohol use, hangovers, and smoking. In addition, the ISQ scores also showed associations with immune biomarkers indicative of systemic inflammation. The review also discusses the strengths and limitations of the ISQ, including its 12-month recall period, which may be adapted in repeated-measures designs. Potential improvements to the ISQ include incorporating additional characteristics such as duration, severity, and impact of immune-related complaints and refining the current scoring method. In conclusion, the ISQ is a simple, cost- and time-effective questionnaire to assess immune fitness. The ISQ can be successfully implemented in research and screening in clinical settings.

Keywords: Immune fitness; Immune status questionnaire; Perceived immunity; Systemic inflammation

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1. Introduction

Immunity is a vital determinant of health and survival.[1] Without a proper immune response, the body cannot defend against various ranges of external pathogens, including bacteria, viruses, fungi, and parasites, as well as environmental toxins.[1] This lack of protection can lead to life-threatening infections.[2] The immune system is also responsible for recognizing disease-inducing changes that occur internally, such as the development of cancer cells.[1] If these changes are not detected by the immune system, they can result in systemic inflammation and the development of immune-related diseases.[2] Conversely, if the immune system becomes overactive and targets healthy cells, this can lead to autoimmune diseases.[2]

Immune fitness refers to the body's capacity to respond to health challenges (such as infections), by activating an appropriate immune response. This is essential to maintain health, prevent, and resolve disease and ultimately maintain or improve quality of life.[3,4] Preventing systemic inflammation is important, as it has been linked to 9 out of 10 most frequently reported causes of death in the United States,[5] including heart disease, cancer, the 2019 coronavirus disease (COVID-19), cardiovascular disease, chronic lower respiratory diseases, Alzheimer's disease, diabetes, chronic liver disease and cirrhosis, and kidney disease.[6-9]

It is estimated that immune-related non-communicable diseases (NCDs) impact approximately 10% of the global population, with the incidence rate continuing to rise worldwide.[5,7-9] According to data from the Global Burden of Diseases Study,[5] the global incidence of six major immune-related NCDs was 67,586,168 cases in 2019. Systemic inflammation can also result from communicable diseases (e.g., viral infections),[10,11] and many patient-reported health complaints in clinical practice (e.g., common cold, headache) are immune-related.[12] The burden of immune-related diseases and complaints highlights the importance of early detection of systemic inflammation and the assessment of immune fitness per se.

Conventionally, immune status is assessed through biomarkers of systemic inflammation in biological matrices such as blood, stool, and saliva.[3,4] These inflammatory markers include C-reactive protein (CRP), fibrinogen, and various cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ.[13,14] Biomarker assessments are usually conducted after consulting a healthcare professional when signs or symptoms of immune-related complaints or diseases are present. It can then be determined whether biomarker concentrations are within the normal range.

Patients are usually unaware of changes in biomarker levels, and objective changes do not always correspond to subjective health perceptions. For example, while inflammation may be present in cases of immune-related complaints, such complaints can also be experienced without any measurable changes in biomarker concentrations.[3,4] Conversely, similar to medical conditions such as hypertension, biomarkers can be out of range even though the patient remains asymptomatic. As a result, correlations between biomarkers of systemic inflammation and immune fitness are often modest.[14] These discrepancies are of concern, as a patient's perception of immune functioning will ultimately determine whether or not medical help is sought (e.g., visiting a physician), and whether behavioral or lifestyle changes are initiated (e.g., quitting smoking). It is therefore critical to assess patient perception of immune status, for example through interviews or questionnaires. Taken together, there is a clear need for alternative assessment tools of immune status, either alone or in conjunction with biomarker assessments. In this context, the immune status questionnaire (ISQ) was developed[15] (Figure 1).

The ISQ was derived from a broader list of 23 immune-related complaints, and regression analysis was conducted to identify the seven primary items that predicted 85% of overall immune fitness (i.e., the sum score of the items).[15] The ISQ is a Likert-type scale that assesses the type and frequency of seven common immune-related complaints, including sudden high fever, diarrhea, headache, skin problems (e.g., acne and eczema), muscle and joint pain, common cold, and coughing (Figure 1). Respondents indicate the frequency of each complaint experienced in the past year using a 5-point Likert scale ranging from 0 (never), 1 (sometimes), 2 (regularly), 3 (often), to 4 (almost always). The sum score of the seven items ranges from 0 to 35 and is converted to a final ISQ score ranging from 0 (very poor) to 10 (excellent) (Figure 2).

The seven validation studies by Wilod Versprille *et al.*,[15] conducted in Dutch or English, revealed that ISQ

Immune Status Questionnaire (ISQ)

Please indicate how often you have had the following complaints **in the past 12 months**:

	Never	Sometimes	Regularly	Often	(Almost) always
Sudden high fever	○	○	○	○	○
Diarrhea	○	○	○	○	○
Headache	○	○	○	○	○
Skin problems (e.g. acne & eczema)	○	○	○	○	○
Muscle and joint pain	○	○	○	○	○
Common Cold	○	○	○	○	○
Coughing	○	○	○	○	○

Figure 1. A sample of the immune status questionnaire

Item sum score	≥15	14	13	12,11	10	9,8	7	6	5	4,3	≤2
Recoded score	0	1	2	3	4	5	6	7	8	9	10

Figure 2. Recoding the sum score of the seven immune status questionnaire items

scores could differentiate between health and disease and correlate significantly with disease severity and mood. The ISQ scores also correlated significantly with a single-item assessment of momentary immune fitness. The validation studies revealed adequate test-retest reliability (r = 0.80). However, since the seven items can occur independently and represent different immune-related complaints, the internal consistency of the ISQ is only modest (Cronbach's alpha = 0.471 – 0.632). This is further reflected by the low inter-item correlations (r < 0.2). Up to now, no attempts have been made to identify a possible underlying factor structure of the ISQ, which could provide more information about the inter-relationship between the items. Finally, a cut-off score of <6 was proposed to indicate reduced immune fitness.

The aim of this review is to provide a complete overview of studies that have utilized the ISQ in research and clinical practice, including validation in various languages. The review discusses the extent to which the ISQ outcomes relate to health and lifestyle factors and immune biomarker assessments. In addition, recommendations are made regarding the use of the ISQ and potential improvements to the current version.

2. Methods

To identify potential studies for this systemic review, a search was conducted on Google Scholar on 19 February 2025 for all publications cited in the ISQ validation study by Wilod Versprille *et al.*[15] The search retrieved 87 publications. Cross-referencing yielded an additional five publications. In total, 92 publications were considered. Of these, 51 publications were included because the ISQ was used in their research, and/or data on the ISQ were presented. The remaining 41 publications were excluded for the following reasons: duplicates (e.g., the same publication or an abstract later published as a full article; $n = 6$), written in Persian or Russian ($n = 2$), the ISQ was not assessed (e.g., the scale was mentioned but no new data was presented; $n = 30$), the publication was not peer-reviewed (e.g., an undergraduate thesis; $n = 2$), or the publication could not be retrieved ($n = 1$).

3. Results

A total of 51 publications were included. In some cases, multiple publications originated from the same study. Overall, data were collected from 37 studies conducted across 14 countries. Most studies originated from Indonesia ($n = 9$) and the Netherlands ($n = 7$), followed by Saudi Arabia ($n = 5$), India ($n = 4$), and the United States ($n = 3$). Other countries represented by one study each included Germany, Greece, Fiji, Italy, Ireland, Jordan, Pakistan, New Zealand, and Malaysia. Five publications presented pooled data analyses incorporating data from multiple countries. The ISQ has been translated into six languages. Most often, the ISQ was administered in English, Dutch, or Bahasa Indonesian. Other studies used unvalidated ISQ versions in Italian, Arabic, and Malay. The sample size ranged from 22 to 45,782 participants, and sample characteristics varied depending on the study objectives. All studies recruited participants aged 18 years and older. The four main sample groups were the general population, student populations, personnel from companies or institutions, and individuals with a diagnosed condition or complaint. Due to the retrospective nature of the ISQ, most of the studies were cross-sectional ($n = 42$), assessing ISQ data at a single time point. Two studies validated the ISQ in the Indonesian language, with one including a test–retest analysis. In addition, seven experimental studies examined ISQ scores changes before and after an intervention.

3.1. Validation studies in other languages

Two validation studies translated the ISQ into Bahasa Indonesian language. Maulana and Arovah[16] tested the psychometric properties of the Indonesian ISQ in 296 adults. They found that the ISQ demonstrated sufficient validity (significant correlations with health-related quality of life assessed using the SF-12), adequate internal consistency (Cronbach's alpha = 0.70 – 0.88), and good test–retest reliability (r = 0.87 – 0.82). In a second, smaller validation study, Azhar *et al.*[17] tested the Bahasa Indonesian ISQ among 30 patients who visited Hasan Sadikin General Hospital for a general health checkup. They concluded that the translated ISQ is a reliable instrument (Cronbach's alpha = 0.706). However, this study did not include a test–retest assessment, and validity was inferred from significant correlations between each individual item and the total ISQ score. The ISQ has also been translated and used in Arabic and Italian. However, no formal validation studies have been published for these language versions.

3.2. Cross-sectional studies relating the ISQ to health and lifestyle correlates

Thirty-seven publications reported survey studies investigating the relationship between ISQ scores and demographic characteristics, health outcomes, disease

states, and lifestyle factors. Abdulahad *et al.*[18] examined irritable bowel syndrome (IBS) complaints among 871 Dutch adults with self-reported insomnia. The online survey, conducted in Dutch, used an earlier ISQ scoring format ranging from 0 (excellent) to 28 (very poor). The presence and severity of IBS symptoms were evaluated using a modified Dutch version of the Birmingham IBS Symptom Questionnaire.[19,20] Poorer ISQ scores were significantly correlated with higher total IBS scores as well as increased reports of constipation, abdominal pain, and diarrhea. Figure 3 shows these correlations after recoding the ISQ scores into the current 0 – 10 scoring format. Poorer immune fitness also correlated significantly with having more frequent nightly awakenings and poorer sleep quality.

Baars *et al.*[21] assessed whether the consumption of fermented milk products was associated with improved immune fitness. A retrospective consumer survey was conducted in Dutch among 390 adults who bought fermented milk products. This early study also used the 0 – 28 ISQ scoring system. The participants reported a significant improvement in immune fitness after beginning consumption of raw fermented milk products. This improvement was observed in both a poor-health group and a normal-health group and was more pronounced in females than males.

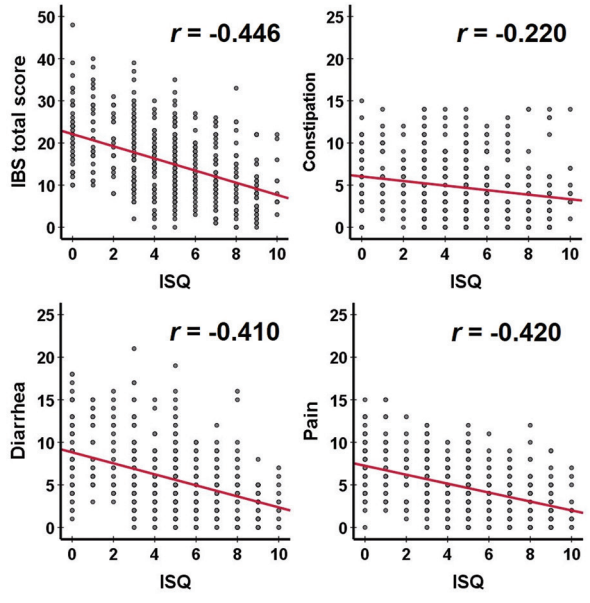

Figure 3. Correlations between the ISQ scores and IBS-related complaints. All Spearman's correlations were statistically significant (p<0.05). Data from Abdulahad *et al.*[18]
Abbreviations: IBS: Irritable bowel syndrome; ISQ: Immune status questionnaire.

Hendriksen *et al.*[22,23] conducted a study among 341 pharmacy students, PhD candidates, and postdoctoral researchers from Utrecht University, the Netherlands, to retrospectively assess the impact of the COVID-19 pandemic on mood and academic performance. An online survey was administered in English or Dutch. Pre-pandemic ISQ scores showed no significant correlations with changes in mood or academic performance during the pandemic – assessed as the average of two lockdown periods. However, further analysis of the 2019 pre-pandemic data[23] revealed that ISQ scores correlated significantly and negatively with stress (r = −0.212, p<0.001), anxiety (r = −0.265, p<0.001), depression (r = −0.204, p<0.001), fatigue (r = −0.244, p<0.001), and loneliness (r = −0.177, p=0.004). ISQ scores were positively correlated with sleep quality (r = 0.210, p<0.001) but showed no significant correlations with optimism, happiness, and quality of life. Using the same dataset, Balikji *et al.*[24] compared participants who reported impaired wound healing (i.e., slow-healing wounds and/or wound infections) with healthy controls. ISQ scores were significantly lower in the impaired wound healing group compared to the control group, particularly on the items assessing diarrhea, headache, skin problems, coughing, and muscle and joint pain.

The study by Hendriksen *et al.*[22,23] was replicated in Germany by Koyun *et al.*,[25] involving 317 young adults (18 – 35 years old) who completed the survey in English. Further analysis of the 2019 pre-pandemic data revealed that ISQ scores correlated significantly and negatively with stress (r = −0.161, p=0.006), anxiety (r = −0.214, p<0.001), depression (r = −0.156, p=0.008), fatigue (r = −0.230, p<0.001), and loneliness (r = −0.144, p=0.015). No significant correlations were found between ISQ scores and optimism, happiness, quality of life, and sleep quality.

Kiani *et al.*[26] examined whether immune fitness in 2019, as measured by the ISQ, could predict the presence and severity of COVID-19 symptoms during the pandemic in the Netherlands. Data were drawn from two studies: the "Corona: How Fit Are You?" study (CLOFIT; n = 1415; Dutch adults)[27] and the Corona Test Street Study (COTEST; n = 88; Dutch adults who tested positive for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]).[28] Alongside immune fitness, various sociodemographic, health, and lifestyle factors were included in regression analyses. For the CLOFIT dataset, ISQ scores before the pandemic were the strongest predictors of both the number and severity of COVID-19 symptoms (explaining 20.1% and 19.8% of the variance, respectively). In the COTEST dataset, pre-pandemic ISQ scores were the only significant predictor of both symptom number (27.2%) and severity (33.1%).

Sips *et al.*[29] examined the impact of reduced immune fitness on work performance. Using data from 425 working adults from the CLOFIT sample,[27] the estimated economic cost of reduced immune fitness for the Dutch economy in 2019 was €10.7 billion. This estimate was based on the average number of absenteeism days (2.9 days per person) and reduced performance (−22.8%) on presenteeism days (19 days per person). The ISQ scores showed a significant negative correlation with the number of absenteeism and presenteeism days as well as with performance levels on presenteeism days. In another CLOFIT subsample ($n = 505$), Hendriksen *et al.*[30] found no significant differences in pre-COVID-19 ISQ scores between participants living alone and those living with family or friends.

Verster *et al.*[4] further examined data from the CLOFIT study to compare the ISQ scores between individuals with and without underlying disease. Participants (n = 1400) reported whether they had any of the following conditions: cardiovascular disease or hypertension, diabetes, liver disease, neurological disease, immune disorders, allergies, kidney disease, pulmonary disease, anxiety, depression, sleep disorders, or other chronic diseases. Of these, 485 reported no underlying conditions, while others reported one (n = 484), two (n = 253), three (n = 108), four (n = 42), or five or more (n = 28). ISQ scores were significantly lower among those with underlying diseases, with scores decreasing further as the number of reported conditions increased (Figure 4).

Other publications confirmed the relationship between ISQ scores and disease state. A comparison between 100 diabetes patients with 100 sex- and age-matched healthy controls from the CLOFIT study revealed that individuals

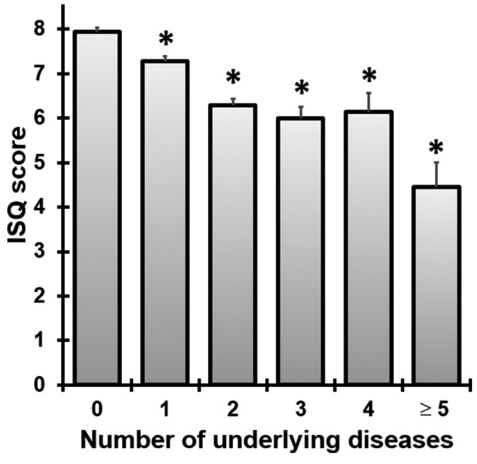

Figure 4. ISQ scores of individuals with and without underlying diseases. Mean and standard errors are shown.
*Indicates significant differences ($p<0.05$).
Abbreviation: ISQ: Immune status questionnaire.

with diabetes had significantly lower ISQ scores.[31] In addition, analysis of 1020 pre-pandemic ISQ scores from CLOFIT showed that 2019 ISQ scores significantly and negatively correlated with both the frequency of common cold episodes in the first 2.5 months of 2020 ($r = -0.212$, $p<0.001$) and the average severity of common cold complaints, as measured by the Jackson Cold Scale ($r = -0.231$, $p<0.001$).[32]

In Greece, Verster *et al.*[33] surveyed 299 international tourists before and after walking the 15.8 km Samaria Gorge. The surveys were completed in English during the bus journey to and from the trail. The data revealed that ISQ scores were a significant predictor of the duration of the walk, with better immune fitness associated with a shorter walking duration and lower water consumption during the hike. However, ISQ scores did not predict exhaustion level, number and duration of breaks, or perceived effort needed to complete the walk. Participants who consume alcohol reported significantly lower ISQ scores compared to non-drinkers.

Tarantino *et al.*[34] examined the impact of perceived stress and immune status on decision-making during the first COVID-19 pandemic lockdown in Italy. A total of 250 adults (aged 19 – 69) completed the ISQ (in Italian), along with the Iowa Gambling Task and a Go/No-Go task. A different ISQ scoring system was used, where higher scores indicated poorer immune status. Younger participants (<34 years old) reported significantly poorer immune fitness than older participants. In addition, females reported poorer immune fitness than males. Poorer immune fitness correlated significantly with greater impulsivity (i.e., disadvantageous decision-making on the gambling tasks) in males but not in females. Adequate immune fitness in younger males was associated with making advantageous choices, whereas poorer immune fitness was associated with making risky, disadvantageous choices in older males.

Kiani *et al.*[35] conducted a pooled analysis of data from 12 studies across various countries to examine the relationship between immune fitness and body mass index (BMI). Data from 4263 adults were included. Compared to individuals with normal weight, ISQ scores were significantly lower among those who were underweight and classified in obesity class III. Using the same pooled dataset, Mulder *et al.*[36] consistently found across all age groups that females reported significantly lower ISQ scores than males, except in the elderly group (≥65 years). The authors proposed that women may report immune-related complaints more thoroughly, including minor symptoms, which could lead to higher overall scores. Interestingly, ISQ scores increased with age, which contrasts with literature

showing age-related decline in immune function.[37] This discrepancy may be due to sampling bias, as online surveys are more likely to attract healthier elderly individuals, thereby skewing results.

Five cross-sectional studies utilizing the ISQ were conducted in Saudi Arabia.[38-42] In one study involving 252 adults, Alfawaz *et al.*[38] administered the ISQ in Arabic and reported a positive significant correlation between ISQ scores and dietary zinc intake. Another survey among 327 adults found a significant positive correlation between ISQ and adherence to the Mediterranean diet.[39] A survey among 1721 national and foreign adult and elderly residents was conducted in both English and Arabic.[40] The study found a significant negative association between ISQ scores and physiological distress during the COVID-19 pandemic, with the strongest effects observed in elderly people. A significant positive association was also found between ISQ scores and the frequency of vitamin D and vitamin C intake. Alharbi *et al.*[41] surveyed 925 national and foreign adult residents and found that having an ISQ score below 6 was significantly associated with obesity, smoking, and a shorter sleep duration. In a separate study, Alharbi[42] surveyed 221 Saudi medical students in both English and Arabic. ISQ scores were significantly and positively correlated with adherence to an exercise program and significantly and negatively correlated with fatty food consumption, daytime sleepiness, and BMI.

In Jordan, Nawaiseh *et al.*[43] conducted a survey among 615 adults (aged 18 – 65) using the Arabic version of the ISQ. A significant positive association was found between ISQ scores and the frequency of vitamin D and vitamin C intake during the COVID-19 pandemic.

Seven studies involving the ISQ originated in Indonesia.[44-50] Ramadhia *et al.*[44] conducted a survey among 47 employees of the Research and Development Agency for Law and Human Rights (Balitbang Hukum dan HAM). ISQ scores, assessed in Bahasa Indonesia, were significantly and negatively correlated with sleep duration ($r = -0.366$, $p=0.011$) but not significantly correlated with dietary nutrient intake (vitamins A, C, D, E, iron, and zinc) and BMI. Purnama and Anindya[45] examined future anxiety among 102 Indonesian nursing students treating COVID-19 patients. The ISQ and survey were completed in Bahasa Indonesia. Future anxiety was assessed with the Future Anxiety Index. Anxiety scores were relatively high among the participants, while 59.8% reported having good immune fitness. No significant relationship was found between the students' ISQ scores and future anxiety, including psychological, social, environmental, economic, media, religious, and general anxiety. Sudrajat *et al.*[46] evaluated 110 adults from the Cibubur Village Community Health Center on immune fitness and attitudes toward herbal consumption during the pandemic. The ISQ (in Bahasa Indonesia) revealed no significant differences in scores based on sex or education. However, participants with jobs had lower ISQ scores than unemployed individuals. Positive associations were found between ISQ scores and age, as well as knowledge and positive attitudes toward herbs.

Chandla *et al.*[47] surveyed 402 COVID-19-positive patients to examine whether ISQ scores differed between symptomatic and asymptomatic individuals. The ISQ, completed in English, showed no significant differences between the two groups.

Purwanto *et al.*[48] conducted a study among 42 Indonesian teachers who followed a community service course involving lectures and daily exercise instructions. ISQ scores, assessed before and after the course in Bahasa Indonesia, significantly improved from 3.48 to 6.64, along with improvements in immune fitness knowledge. In a related study, Purwanto *et al.*[49] examined 170 Indonesian medicine and health science students and found that males reported better immune fitness than females. In addition, regular sports participation was associated with higher ISQ scores and lower incidences of headaches, skin problems, and muscle and joint pain. Finally, Susmitha and Simamora[50] surveyed 120 Indonesian law students and found that better knowledge of infectious diseases and immune fitness was strongly correlated with higher ISQ scores ($r = 0.782$).

In Pakistan, Kazmi and Iftikhar[51,52] examined biopsychosocial determinants of quality of life in 400 patients with hepatitis B or C. In addition to the ISQ, quality of life, mood, and personality were assessed. Regression analysis identified ISQ scores as significant predictors of quality of life. Significant negative correlations were found between ISQ scores and various dimensions of psychological distress, including depression, anger, mania, anxiety, suicidal ideation, psychosis, sleep and memory issues, repetitive thoughts and behaviors, dissociation, personality functioning, and mental resilience.

In the United States, Huang *et al.*[53] examined physical activity, immune fitness, and quality of life during the COVID-19 pandemic in a sample of 467 adults aged over 20. The survey was conducted through the Amazon Mechanical Turk platform in English and the ISQ was assessed for the past 6 months. Based on their score on the international physical activity questionnaire-short form,[54] participants were categorized into active or sedentary groups. Regression analysis revealed that better immune fitness was a significant predictor of an active lifestyle during the pandemic. However, ISQ scores were not a significant predictor of a sedentary lifestyle.

Billot *et al.*[55] examined the relationship between anxiety and immune fitness among 390 residents of New Zealand, including indigenous Māori participants aged 19 – 88 years. The survey was conducted in English. In both Māori and non-Māori participants, higher anxiety levels were strongly linked to poorer immune fitness as measured by ISQ scores.

Breeze *et al.*[56] combined data from the general population and university students in Italy, New Zealand, and India (n = 2,482) and also found that anxiety was significantly and negatively correlated with ISQ scores. Further network analysis by Chalmers *et al.*[57] confirmed this finding, revealing that anxiety scores were also positively correlated to depression and stress. Among these variables, stress but not depression was directly correlated to poorer immune fitness. While mindfulness, mental resilience, and positive affect were positively associated with quality of life, none of these were direct predictors of immune fitness. Notably, quality of life was positively related to immune fitness in participants from New Zealand and India, but not Italy, suggesting that cultural differences may influence these relationships. In terms of demographics, sex emerged as a relevant factor: females in New Zealand and Italy had significantly lower ISQ scores compared to males, a pattern not observed in India.

Holland *et al.*[58] investigated the relationship between immune fitness and cognitive functioning in long COVID-19. The study was conducted among 71 Irish long COVID-19 patients and 50 healthy controls. Participants completed the ISQ along with questionnaires assessing anxiety, depression, fatigue, and cognitive functioning (i.e., absent-mindedness, slips and errors of perception, memory problems, and psychomotor impairment) using the Cognitive Failures Questionnaire (CFQ).[59] The long COVID-19 patients had significantly poorer immune fitness than the control group (mean ISQ score: 4.36 versus 8.97, p<0.001) and reported more cognitive difficulties, including higher scores on depression and fatigue. Regression analysis revealed that immune fitness significantly predicted cognitive functioning (CFQ score), even after controlling for depression, fatigue, and other risk factors such as BMI, sex, and age. In contrast, a Dutch study by Kiani *et al.*[60] involving 299 long COVID-19 patients found that pre-infection ISQ scores (for the year before SARS-CoV-2 infection) did not significantly predict fatigue, mood, and immune fitness during long COIVID-19.

Verster *et al.*[61] conducted a study among 333 international young adults (aged 18 – 35) visiting Fiji for work or holiday, examining the impact of the change in environment on immune fitness. The survey was conducted in English. ISQ scores significantly improved while participants were in Fiji – regardless of the purpose of visit. The same cohort was also analyzed for alcohol consumption and hangover severity.[62] Results showed that subjective intoxication was the strongest predictor of next-day hangover severity. ISQ scores also significantly contributed to this prediction model, especially among women. However, ISQ scores did not predict subjective intoxication levels or the quantity of alcohol consumed. Further analysis of the Fiji dataset revealed significant correlations between ISQ scores and various mood states experienced at home, including stress (r = −0.183, p<0.001), anxiety (r = −0.145, p=0.008), depression (r = −0.148, p=0.007), fatigue (r = −0.148, p=0.007), loneliness (r = −0.144, p=0.015), and neuroticism (r = −0.250, p<0.001). No significant correlations were found between ISQ scores and hostility.

3.3. Relationship with momentary immune fitness

The assessment of current, momentary immune fitness is usually conducted with a single-item rating scale, ranging from 0 (very poor) to 10 (excellent) (Figure 5). A definition of immune fitness is provided to aid participant understanding. In several studies, past year's immune fitness, as assessed by the ISQ, was compared with current immune fitness.

The validation studies by Wilod Versprille *et al.*[15] reported significant but modest correlations between ISQ scores and current immune fitness (r = ~0.4). Other studies have also investigated the predictive validity of past year's immune fitness (ISQ) for current immune fitness, generally finding modest correlations. In a study by Mulder *et al.*,[14] data from 108 Dutch students revealed a significant correlation between ISQ scores and a momentary single-item immune fitness rating (r = 0.452, p<0.001).[63] Significant correlations were specifically found between current overall immune fitness and the past-year frequency of experiencing fever, headache, and common cold. Other immune-related complaints assessed by the ISQ did not show significant correlations. A pooled analysis from multiple studies,

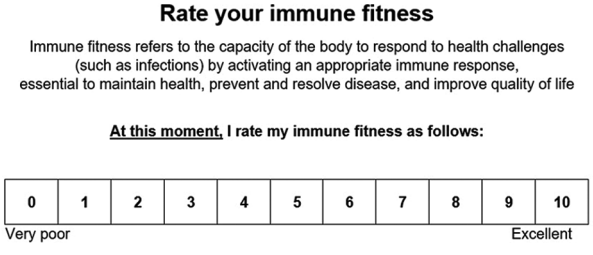

Figure 5. A sample of the single-item assessment for current, momentary immune fitness. Adapted from Verster *et al.*[3]

with a combined sample size of 3,748 participants, revealed a significant and positive correlation between ISQ scores and current immune fitness (r = 0.407, $p<0.001$).[3] Another pooled analysis involving 4,272 participants showed a significant positive correlation between the ISQ score and a single-item assessment of general health (r = 0.593, $p<0.001$).[3]

3.4. Relationship between ISQ scores and immune biomarker assessments

To date, only a few studies have investigated both immune biomarkers and ISQ scores. Mulder *et al.*[14] tested 108 Dutch students aged 18 – 30 years, who completed several questionnaires on mood and health, including the ISQ. Momentary immune fitness was assessed using a single-item rating scale ranging from 0 (very poor) to 10 (excellent) (Figure 5). Participants provided saliva samples for the determination of IL-1β, IL-8, immunoglobulin A (IgA), and CRP. No significant correlations were found between momentary immune fitness and these biomarkers. Further analysis of this dataset by Balikji *et al.*[64] confirmed a significant correlation between ISQ scores and momentary immune fitness (r = 0.452, $p<0.001$). Participants were divided into two groups: an impaired wound healing group (n = 30; self-reported slow healing wounds and/or wound infection in the past year) or a healthy control group (n = 78; self-reported normal wound healing). The impaired wound healing group had significantly lower ISQ scores compared to the control group (5.2 and 6.4, respectively, p=0.009). However, no significant difference was observed between the groups for momentary immune fitness (7.3 and 7.7, respectively, p=0.087). Among the healthy controls, no significant correlations were found between ISQ scores and immune biomarkers. In contrast, for the impaired wound healing group, ISQ scores showed significant positive correlations with IL-1β (r = 0.439, p=0.015) and IL-8 (r = 0.393, p=0.032) (Figure 6). In addition, a significant positive correlation was found between momentary immune fitness and saliva IgA concentrations (r = 0.383, p=0.037).

Authors of two additional studies that assessed biomarkers[65,66] were contacted with a request to share their datasets for further analysis of the relationship between ISQ scores and immune biomarkers. However, no responses were received.

3.5. Randomized controlled trials and other intervention studies

To date, seven experimental studies have included ISQ assessments, with four of these studies conducted in India. Thakar *et al.*[67] conducted a multicenter, prospective open-label study among 20,574 Indian adults (aged 18 – 68 years) who had medium-to-high exposure risk to SARS-CoV-2 infection, such as healthcare workers. Participants were asked whether they would like to receive prophylactic Ayurvedic medication to reduce the risk of SARS-CoV-2 infection. Those who opted for it formed the intervention group (n = 15992) and were administered Guduchi Ghanavati (1 g daily for 28 days) in addition to standard preventive guidelines (SPG), including frequent hand washing, physical distancing, and using face masks. Participants who declined the Ayurvedic medication formed the control group (n = 4953) and received the SPG only. The ISQ and World Health Organization Quality of Life-BREF (WHOQOL-BREF) instrument[68] were administered at baseline and after 28 days. The baseline ISQ scores were 9.3 for the intervention group and 9.14 for the control group, suggesting raw scores were used without converting to the standard 0 (very poor) to 10 (excellent) scale. No significant difference in COVID-19 infection rates was found between the groups. Both groups showed improvements in ISQ scores and quality of life, with a statistically significant but small ISQ increase in the intervention group (+0.30 units) compared to the control

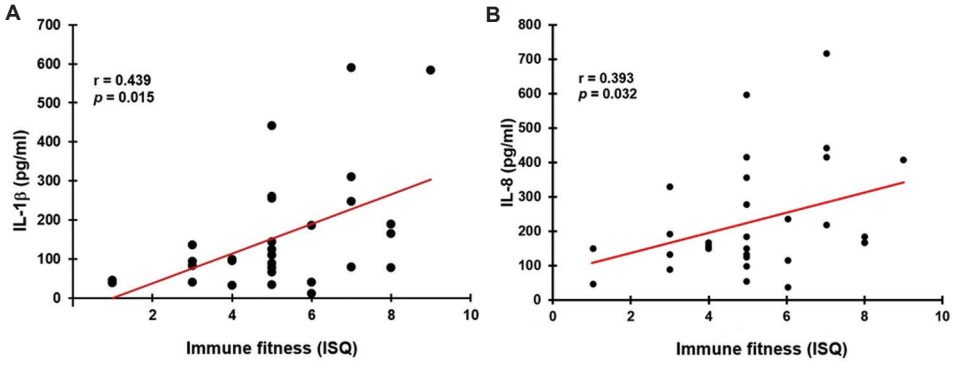

Figure 6. (A and B) Relationship between ISQ scores and saliva immune biomarkers. Data from Balikji *et al.*[64]
Abbreviation: ISQ: Immune status questionnaire.

group (+0.11 units). At baseline, weak but significant correlations (r < 0.25) were found between ISQ scores and all domains of the WHOQOL-BREF. Notably, the ISQ score correlated significantly (r = 0.83) with a single-item general health rating on a 0 – 10 scale.

Nesari *et al.*[65] conducted a prospective, open-label study in India to evaluate the impact of Ayuraksha on immune fitness and SARS-CoV-2 infection rates. A total of 80,000 Delhi police personnel were invited to participate. They received an Ayuraksha kit containing Samsamani Vati, Anu Taila, and Ayush Kwatha. Among them, 45,782 completed a baseline ISQ assessment, with follow-up assessments after 60 days (n = 39,880) and 90 days (n = 32,062) of daily treatment. Surveys were completed in English through Google Forms. The ISQ assessed immune fitness over the past 12 months. Momentary immune fitness was assessed with a single-item assessment on a 0 – 10 scale (Figure 5), while reduced immune fitness was assessed with a yes/no question (Figure 7).

Mean ISQ scores were 9.53 at baseline, 9.61 after 60 days, and 9.54 after 90 days, suggesting self-reported immune fitness was very high (>9). The authors were contacted to clarify whether these scores reflected recoded ISQ values or raw sums and to request further analysis of the dataset; however, no response was received. The lack of significant improvement in ISQ scores over time may be due to a ceiling effect, given the initially high scores. A methodological concern is that ISQ assessments at each follow-up still covered the 12-month period prior, thus overlapping substantially with the pre-intervention phase. This undermines the ability to detect change attributable solely to the intervention. The momentary immune fitness was also very high at each time point: 9.17 at baseline, 9.26 after 60 days, and 9.34 after 90 days. These scores also showed no significant improvement over time. However, the percentage of participants reporting reduced immune fitness progressively decreased from 5.25% at baseline to 3.76% after 60 days and 2.74% after 90 days.

In the second part of the study, a subsample of 101 participants who agreed to take Ayuraksha for 60 days was compared to a control group of 66 participants who declined the intervention. Blood samples were collected

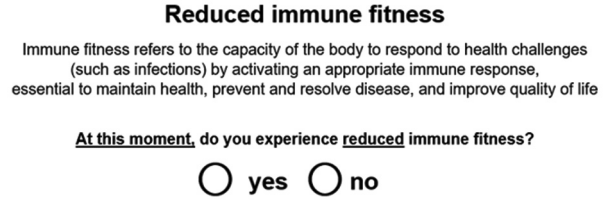

Figure 7. A sample of yes/no binary assessment of reduced immune fitness. Adapted from Verster *et al.*[3]

at baseline and after 60 days for the analysis of immune biomarkers, including CRP, IL-2, -4, -6, -10, and -12, as well as IgG, IgM, IgA, CD3, CD4, and CD8. Immune fitness was assessed using both the single-item scale and the ISQ. The mean age of participants was 39 years, with the majority being male (97.5% of the intervention group and 90.9% of the control group). The percentage of participants who tested positive for SARS-CoV-2 during the study period was significantly lower (p=0.003) in the intervention group (17.5%) compared to the control group (39.4%). ISQ scores in the intervention group improved slightly from baseline (9.30 ± 1.28) to day 60 (9.51 ± 1.08), but the difference was not statistically different. The control group also did not demonstrate statistically significant changes in the ISQ scores. Notably, the ISQ assessed immune fitness for the prior 12 months, thereby including 10 months of pre-intervention data in the day 60 assessment. Similarly, the increase in momentary immune fitness in the intervention group – from 8.84 ± 1.1 to 9.04 ± 1.2 – was not statistically significant nor was any change observed in the control group. These subjective assessments were mirrored by the biomarker data, which showed no significant change in the intervention group. Interestingly, in the control group, IL-6 levels were significantly elevated at day 60. However, the study did not report correlations between perceived immune fitness and immune biomarkers.

In Bengaluru, India, Wadud *et al.*[69] examined the prophylactic effect of a Unani poly-herbal decoction and Khamira Marvareed (herbs-mineral preparation) in 4,500 individuals at risk for SARS-CoV-2 infection. In this randomized, controlled, prospective field study, participants in the intervention group received an oral combination Unnab (*Ziziphus jujube* Mill.), Sapistan (*Cordia myxa* L.), Behidana (*Cydonia oblonga* Mill.), and *Khamira Marwareed* for 20 days, while the control group received no treatment. Assessments were made at baseline and on day 20 through in-person visits, with a telephone follow-up after 35 days. The ISQ and WHOQOL-BREF[68] were used to evaluate immune fitness and quality of life, respectively. Of the total sample, 2,240 participants of the intervention group and 2,073 controls (no intervention) completed the study. Compared to the baseline, the ISQ scores and quality of life improved significantly in the intervention group compared to the control group which showed no significant changes. However, infection rates did not differ significantly between the groups.

Khadke *et al.*[66] conducted a single-blind, randomized, placebo-controlled trial in 28 healthy Indian volunteers to examine the antioxidant and anti-inflammatory properties of a prophylactic polyherbal formulation (PPHF; Kofol immunity tablets). The treatment group (n = 18) received PPHF twice daily for 2 months, while the control group (n = 10) received a matched placebo. The formulation

contained Triphala Guggul, Guduchi (*Tinospora cordifolia*), Haridra (*Curcuma longa*), Manjishtha (*Rubia cordifolia*), Chitrak (*Plumbago zeylanica*), and Trikatu (a combination of *Zingiber officinale*, *Piper nigrum*, and *Piper longum*). Assessments included the ISQ, perceived stress, WHOQOL-BREF, and blood biomarkers such as $CD4^+$, $CD8^+$, IFN-γ, TNF-α, IL-10, malondialdehyde (MDA), and glutathione peroxidase (GPx). PPHF significantly increased ISQ scores, reduced stress, and improved quality of life compared to the placebo group. Biochemical analysis showed decreased MDA, increased GPx, decreased TNF-α, and increased IL-10 in the PPHF group. However, the authors did not provide their dataset, precluding further analysis of correlations between ISQ scores and biomarkers.

In the USA, Stefan *et al.*[70] conducted a randomized, double-blind, placebo-controlled trial to examine the effects of exogenous beta-hydroxybutyrate supplementation – a proxy for a ketogenic diet – on safety and health metrics. Participants in the intervention group consumed 12.75 g of beta-hydroxybutyrate salts twice daily for 90 days, while the control group received a maltodextrin placebo. ISQ scores were assessed at baseline and at 30, 60, and 90 days. No significant differences in ISQ scores were observed between the groups or across time points.

In Malaysia, Goh *et al.*[71] conducted a randomized controlled trial to investigate the effects of combined supplementation with lutein, zeaxanthin, and elderberries on ocular health and immune fitness in 110 healthy volunteers. The intervention group (n = 51) received the product daily for 20 days, whereas the control group (n = 50) received a placebo. Ocular health was assessed using the ocular surface disease index, and immune fitness was assessed with the ISQ. Compared to the placebo group, a significant decrease in ocular complaints was reported by the intervention group. The intervention group also exhibited a 15.9% improvement in ISQ scores (from 7.92 to 9.18). Since the placebo group's ISQ scores also improved (from 7.90 to 8.69), between-group differences in immune fitness were not statistically significant. Correcting sex, age, and BMI as a covariate did not change the findings.

In an open-label study, Harinath *et al.*[72] examined the effects of low-dose naltrexone on immune fitness in 665 American adults with a mean age of 54 years (range: 19 – 96). ISQ was assessed at baseline and after 3 months (range: 89 – 425 days). ISQ scores were recoded according to Wilod Versprille *et al.*,[15] but multiplied by a factor 10 – yield a score range from 0 (very poor) to 100 (excellent). A 16.7% improvement (from 59.3 at baseline to 69.2 after 3 months) in ISQ scores was recorded.

4. Discussion

The studies summarized in this review demonstrate that the ISQ is a valid and reliable tool for assessing immune fitness. The studies confirmed significant correlations between ISQ scores and known factors that can influence immune fitness, including demographics (e.g., sex and age), lifestyle factors (e.g., daily diet, physical exercise, and smoking), mood and personality (e.g., stress, anxiety, and neuroticism), and health correlates (e.g., BMI or presence of underlying disease). An overview of key correlations is presented in Figure 8.

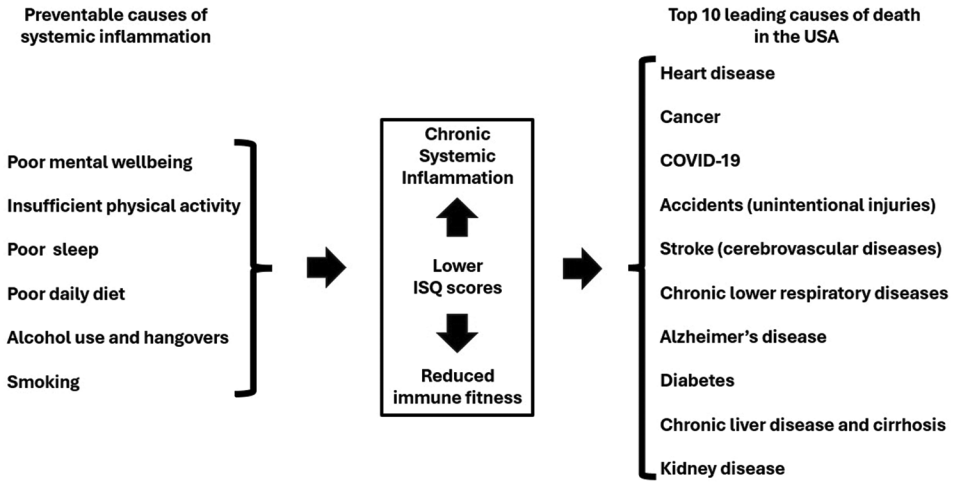

Figure 8. The relationship between ISQ scores, systemic inflammation, and the top ten leading causes of death in the United States. This conceptual model illustrates how preventable lifestyle-related risk factors can lead to chronic systemic inflammation, which is associated with lower ISQ scores and reduced immune fitness. Reduced immune fitness may increase vulnerability to various diseases, including several of the top ten leading causes of death. Abbreviations: COVID-19: 2019 coronavirus disease; ISQ: Immune status questionnaire.

Figure 8 also highlights the top ten causes of death in the United States,[5] many of which are linked to impaired immune fitness. Studies have consistently shown that individuals with these conditions tend to report lower ISQ scores compared to healthy controls. Moreover, individuals who self-report poor immune fitness (through a binary yes/no question) also show significantly lower ISQ scores. Past-year immune fitness scores derived from the ISQ were strongly correlated with momentary assessments. In addition, in patient groups with impaired immune fitness, ISQ scores were significantly associated with biomarkers of systemic inflammation.

4.1. Strengths of the ISQ

In addition to the significant correlations with lifestyle and health outcomes that demonstrate the validity of the ISQ, the questionnaire has several advantages over other measures such as biomarker assessment. First of all, the ISQ is a very short questionnaire. It contains only seven items that are easy to understand and can be completed in under a minute. Unlike biomarker assessments, which are time-consuming and often require costly laboratory facilities, ISQ involves minimal costs and a short duration of testing.[3,4] The ISQ's simple structure – listing common immune-related complaints and their frequency – makes it easily translatable without compromising its psychometric properties. This is supported by successful validation studies in Indonesian populations.[16,17] These advantages make the ISQ a practical tool not only for research but also for routine health screening in clinical and community settings.

4.2. The concept of immune fitness

Immune fitness is a complex concept that is not fully captured by the current version of the ISQ.[4] As demonstrated in this review, various demographics, mood, personality, and health metrics influence overall immune fitness. In addition, there are several characteristics of immune-related complaints next to their frequency of occurrence that has an impact on overall immune fitness. These characteristics are summarized in Figure 9.

As is evident from Figure 9, the ISQ covers only the type and frequency of occurrence of a selected number of immune-related complaints. First of all, there are many more immune-related complaints than the seven items covered by the ISQ. When developing the ISQ, a list of 23 immune-related complaints was reduced to the seven most common complaints that predicted 85% of the total score.[15] The actual frequency of occurrence of the items was not scored due to several reasons. First of all, for several items (e.g., common cold or diarrhea), this could introduce recall bias, which would likely register a lower score when using the five-point Likert scale. Second, some other items (e.g., joint and muscle pain or skin problems) may have fluctuating symptoms, making a numerical scoring less useful. However, the ISQ does not account for several important aspects of immune-related complaints, such as the duration and severity of the symptoms and their impact on daily activities and quality of life.

Theoretically, it is assumed that a single-item overall assessment of immune fitness will automatically take

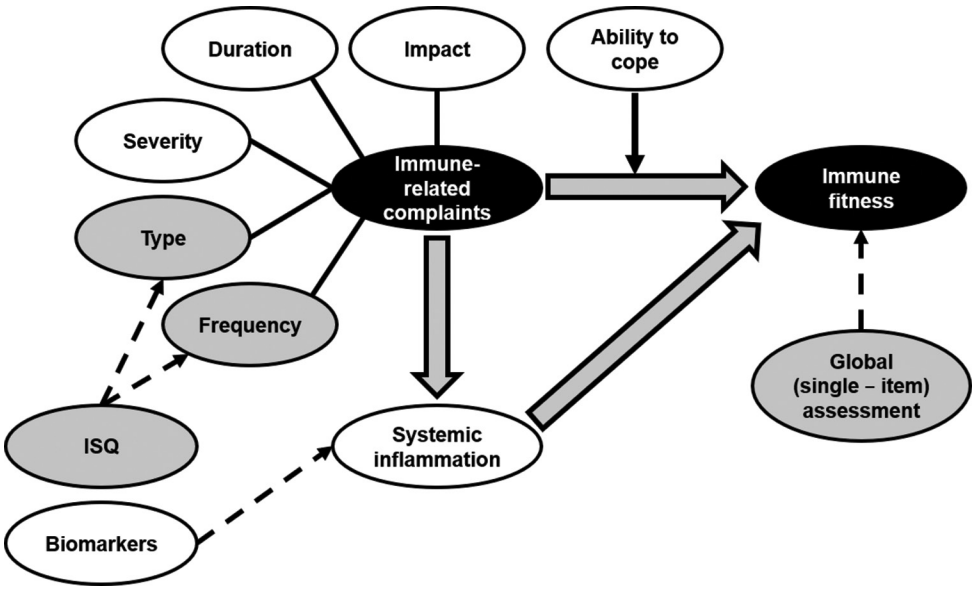

Figure 9. Factors contributing to the perception of immune-related complaints and immune fitness
Abbreviation: ISQ: Immune status questionnaire.

into consideration all factors that are summarized in Figure 9.[4] The US Food and Drug Administration supports the use of single-item assessments over multiple-item questionnaires,[73] as the composite scores from the latter can never provide a complete overarching global assessment of the concept.[4,73] However, although a single immune fitness score theoretically includes all the relevant factors, such an assessment provides no information on the nature, severity, or specific cause of immune-related complaints. Therefore, research is currently in progress to determine if the current ISQ can be improved by incorporating some of these relevant factors. It is also important to recognize the limitations of biomarker assessments. While biomarkers offer objective evidence of inflammation or immune activation, they reflect only a narrow slice of the immune system's functioning. Typically, studies measure a limited panel of biomarkers, which may or may not be indicative of overall immune status. Moreover, many biomarkers provide no information about how immune issues are experienced by individuals – such as the duration or impact of symptoms. Biomarkers can also change without being noticed by patients, similar to asymptomatic hypertension. Therefore, biomarkers should be considered as supportive evidence for the assessment of overall immune fitness, but not vice versa.

4.3. Scoring of the ISQ

Another aspect of the current ISQ that might need revision in the future is its scoring system (Figure 2). The current scoring of items ranges from 0 to 4, yielding a raw sum score from 0 to 28, which is then recorded into a score of 0 (very poor) to 10 (excellent). At first glance, this final score is easy to interpret. For example, in the validation article,[15] scores below 6 were interpreted as indicating reduced immune fitness. However, after using the ISQ in various studies and discussing the outcomes with both study participants and academic colleagues, it appears that a cut-off score is not warranted. The latter is also true for single-item assessments of overall immune fitness.[3] Immune fitness is a relative perception that varies by individual. For example, an elite athlete may report a baseline score of 9, corresponding to peak performance. If they later report a 7, this reflects a perceived reduction in immune fitness – even though 7 is still considered a "healthy" score. Thus, a score interpreted in isolation may not accurately reflect a change in health status. To address this, researchers are encouraged to assess reduced immune fitness separately using a simple yes/no question.

Another issue with the current scoring approach is that all seven immune-related complaints are weighted equally. However, some of the complaints may have a greater impact on overall immune fitness and well-being than others. For example, having a headache is likely to have a bigger negative impact on daily activities than coughing. Furthermore, scores of some items correlate with each other, while others do not.[15,16] Therefore, previous studies have proposed differentially weighting the scores of the ISQ items.[16] Future research should determine whether this strategy will result in a relevant improvement of the ISQ.

As illustrated in Figure 9, overall immune fitness is influenced by more than just the type and frequency of seven specific complaints. This broader complexity likely explains why correlations between ISQ scores and single-item overall immune fitness scores are not perfect ($r = 0.4$).[3] Hence, it is important to re-evaluate the current ISQ scoring format, considering possible adaptations to better match global immune fitness assessments.

4.4. Recommended use of the ISQ in experimental studies

In experimental studies, the ISQ is very suitable for assessing baseline or pre-intervention immune fitness. However, it is important to recognize that the ISQ reflects the past year's immune fitness. If the goal is to measure current or momentary immune fitness, other assessment tools such as the single-item immune fitness scale (Figure 5) or the yes/no reduced immune fitness question (Figure 7) are more suitable.

The original ISQ measures the occurrence of immune-related complaints over the past 12 months. Depending on the study design, this time period can be adjusted. For example, it can be reduced to the past three or 6 months. Naturally, the shorter the period assessed, the fewer complaints participants are likely to report – thus yielding higher ISQ scores. Conversely, if the recall period is too short, participants may not have experienced any complaints, which limits the questionnaire's informativeness. We propose that the minimum recommended timeframe for the ISQ should be 4 weeks. However, this needs to be validated in prospective studies, which should also explore whether the scoring system should be adjusted for shorter recall periods (e.g., reporting the number of days a complaint was experienced instead of using a Likert scale). If assessments are needed for very short timeframes (e.g., <1 month), a better alternative may be the single-item immune fitness scale. This tool allows researchers to modify the reference period (e.g., "At this moment" or "During the past 2 weeks") to capture more immediate perceptions of immune fitness.

In the experimental studies reviewed here, the ISQ was administered without adjusting its 12-month recall period. This approach introduces bias in the study outcome. For example, if the ISQ is completed at baseline (visit 1), and again at 30 days (visit 2), 60 days (visit 3), and 90 days (visit 4), subsequent assessments still reflect immune

complaints experienced before the intervention began (i.e., 9 – 11 months prior). If the goal is to monitor monthly changes, a tool designed for shorter recall – such as a past-month single-item immune fitness assessment – would be more appropriate.

4.5. Use of the ISQ in clinical practice

Although not documented in scientific literature, the ISQ is also used in clinical practice. An online search revealed various examples of physicians using the ISQ for screening or educational purposes.[74,75] For example, the Arizona Family Health Centre offers the ISQ on its website,[74] alongside blogs and a video explaining immune health and strategies for improvement. In cases where patients score poorly – indicating reduced immune fitness – further medical evaluation may be warranted. However, it is important to note that such websites clearly state that the ISQ is used for informational and educational purposes only and is not intended to provide medical advice or replace consultation with a healthcare professional.

Another example comes from the Oak Wellness Hub from Ghana, Africa, which used the ISQ to increase public awareness of immune health during the COVID-19 pandemic.[75] Their website combined the ISQ with lifestyle-related questions, enabling patients to evaluate their immune status. The website invited people with the tagline: "discover your immune status in <5 min." One patient who completed the questionnaire reported: "*This questionnaire helped allay my fears when the COVID-19 pandemic hit. When I got a suboptimal score. I was alarmed. I thought I was doing so well in keeping healthy. This great tool and its rich resources educated me on what to do and strengthened my resolve to boost my immunity.*"[75] Of importance, the website emphasized that their questionnaire was intended as a screening guide and not a replacement for professional medical assessment.

Online screening tools like these can help patients evaluate their immune fitness and make informed decisions about seeking medical attention or adjusting their lifestyle. Importantly, the ISQ is freely available for public use and distribution, making it a valuable tool for individuals and countries with limited financial resources.

5. Conclusion

In the 5 years since Wilod Versprille *et al.*[15] developed the ISQ, a total of 38 studies (51 publications) have implemented the questionnaire in their research. These studies have shown that the ISQ is a reliable, valid, and cost-effective tool. It is also an easy-to-understand questionnaire consisting of seven items that can be completed within a short time. The ISQ has been implemented in different types of studies and clinical settings and has been translated and validated in different languages.

The studies described in this review demonstrated that the ISQ scores are related to demographics (e.g., sex and age), mood, personality, disease states, health correlates, and lifestyle factors. In addition, ISQ scores exhibited a correlation with immune biomarker concentrations. The ISQ has been used in multiple cross-sectional surveys and a limited number of experimental studies – either to assess baseline immune fitness or monitor intervention effects such longitudinal studies, the original 12-month recall period may be adjusted to a shorter time period. Based on the current review, a minimum recall period of 4 weeks may be appropriate, though further research is needed to confirm this. For shorter periods, the single-item global immune fitness scale is recommended instead.

Beyond research, the ISQ is increasingly being used in clinical practice for routine screening. It offers patients and clinicians a quick, affordable, and personalized snapshot of immune health, which can help guide decisions on whether further evaluation (e.g., lifestyle assessment, physical examination, or biomarker testing) is warranted.

Future research should explore potential improvements of the ISQ, such as incorporating additional aspects of immune-related complaints such as duration, severity, and impact and refining the scoring system to better capture overall immune fitness. Notwithstanding these opportunities for improvement, the ISQ has already established itself as a practical and informative tool for assessing immune fitness in both research and clinical settings.

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Conflict of interest

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Author contributions

Conceptualization: All authors
Visualization: Joris Verster
Writing–original draft: Emina Išerić, Joris Verster
Writing–review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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REVIEW ARTICLE

A new paradigm: Edith Stein's empathy and expert knowledge in psychosomatic conditions

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Abstract

Researchers in the developing science of psychology initially adopted a naïve realist stance. In recent years, there has been a shift toward more nuanced positions, accompanied by new requirements in professional ethical codes. These developments have been influenced by social movements and associated changes in power dynamics within health, education, and social welfare. Changing views in the philosophies that underpin social science, along with the rise of social media, are also contributing factors. Psychological researchers have worked to understand the human condition by proposing and testing their models. However, new guidelines now require that they operate within the limits of their expertise. If they are to conduct research on a group of people who suffer from a specific health condition, they must include individuals affected by that condition as stakeholders. This represents a shift in which the expert's ability to know what is going on in the mind of another person is increasingly questioned. The phenomenon of psychosomatic illness has long prompted tensions in the relationship between expert professionals and those who are suffering. However, there is now a further undervaluing of expert knowledge, alongside the growing expectation that individuals' beliefs about their own suffering are just as valid as anyone else's. Researchers must adopt a more empathetic stance, such as the one described by Edith Stein. Practitioners will need support in responding to these evolving expectations. Some examples of successful adaptations to these changes include the concept of neurodiversity and the recovery philosophy.

Keywords: Psychosomatics; Research ethics; Knowledge construction; Empathy; Phenomenological theory; Edith Stein; Recovery model; Post-colonial studies

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1. Introduction

Kuhn[1] observed a tendency for science to shift between paradigms. His critique included the observation that knowledge constructions do not adequately capture all the complexities of reality, leading to occasional shifts to new positions. These shifts can be understood as attempts to overcome the shortcomings of previous theoretical models. An awareness of such shortcomings is expressed when researchers articulate their ontological and epistemological positions.[2] Differences in how knowledge is gained are complex, and there has always been a mix of theoretical positions in psychology. However, the boundary of what is accepted as valid science has changed.[3]

The field of psychology emerged as an independent discipline in the 19th and early 20th centuries, and from the start, most psychological researchers would have adopted a naïve realist epistemological position.[4] They would have believed that the measures they used were establishing universal truths about the human condition. Following the changes explored in this article, it is now likely that most psychological researchers adopt something akin to a critical realist position.[2] The possibility of truth is not denied; rather, there is a recognition that we cannot know reality directly in all its range and complexity. This shift, however, is not occurring in mainstream medical research, where knowledge construction has a more direct and verifiable connection with material biological reality.

Psychosomatic health problems have been characterized as "anything that cannot be explained by organic factors…".[5(p377)] This means that when human suffering is not found to have a material biological cause, conflict is likely to arise between the expert practitioner and the patient. The expert cannot validate the patient's suffering as a simple "biological reality," and psychological understandings are brought into play. The body is understood to be a part of the material world and is thus subjected to cause-and-effect relationships, making it amenable to study within a relatively simple realist epistemological stance. The mind, by contrast, is thought of as separate, with a potential for autonomous action expressed in behaviors that are freely chosen.[6,7] Psychosomatic problems, then, have an ambiguous quality, falling somewhere between the medical and moral spheres of understanding.[8]

If a condition is found to have an organic cause, treatment and management then become the responsibility of health professionals. However, when the cause is psychological, the person who is suffering retains much more responsibility. For example, psychosomatic conditions, such as tinnitus and chronic pain may be labeled as psychopathological, or not, in ways that are unhelpful to the person who is suffering.[9] Similarly, understandings of the condition of chronic fatigue have shifted, introducing narratives that do not align well with lived experience.[10] If chronic fatigue is validated as a medical condition, the person's hope for recovery can be unhelpfully diminished. If it is not, the person may be seen as malingering, and there is then a risk that psychological understandings might lapse into moral judgments, especially if it is believed that the person is choosing to live in a manner that is damaging their health, or that they deny their potential for healthy living. The philosophies underpinning these distinctions are founded on a split between mind and body, yet this split does not exist in the ontological realm.[8] We can therefore continue to entertain the possibility that there is one reality across both medical and moral spheres, and that truths can be established by examining that reality, truths that are apolitical and formulated independently of any moral judgment. This is achieved not by separating the psychology of the mind from the judgment of the social moral order, but by examining both as aspects of a connected lived experience.

For psychological research to retain its status as a science, practitioners must avoid moral judgments, and the guidance provided by regulatory bodies has changed to uphold that principle. In contemporary ethical guidance,[11,12] researchers are now required to attend to the rights of their participants. These rights are recognized in relation to dignity and respect for difference. For example, the terms "gender identity" and "culture" were added to the American Psychological Association (APA) Ethical Principles of Psychologists and Code of Conduct,[11] along with a new principle, "D: Justice," emphasizing the rights of all people. This is also reflected in the requirements of the university Human Research Ethics Board, in standards, such as: "Justice refers to fairness and equitable treatment. No specific populations should be burdened as specific recipients of the harms in research, or denied the benefits of research or research knowledge."[13(p2)]

The BPS Code of Human Research Ethics Guidance also notes that changes are required: "It is now common practice to refer to a person who provides data for research as a "participant." This recognizes their active role and replaces the term "subject," which has been viewed as portraying people as passive rather than active agents."[12(p5)]

Requirements include the expectation that psychological researchers may need to consult "stakeholders" – that is, people who will be affected by the outcomes of their research.[12,13] This is particularly important in nations where Indigenous populations have specific needs and rights, such as in New Zealand.[14]

Researchers are also expected to examine their own motivations and interests, identify any potential for bias, and use reflexivity to situate their research.[15] This reflexivity is required because description and interpretation can be influenced by narrow cultural moral judgements.[15] Ethical codes also require that practitioners work within the limits of their professional expertise.[11,12] In this sense, it is understood that psychological researchers cannot know reality in all its complexities, and must consult with others where their own knowledge is lacking.

Researchers in psychology will be aware of a philosophical turn toward a constructivist position, in which knowledge is seen as local and contingent.[16] This shift is also reflected in popular culture, where there is

increasing talk of a "post-truth world," a world in which reality is seen as no more than what each person claims it to be.[17] We are currently witnessing some unfortunate outcomes of this shift, for example, in the dismissal of evidence for the safety and effectiveness of vaccines.[18] These cultural changes, in which expert knowledge is devalued, are associated with a dramatic transformation in how people access information.[17] Before the development of social media, academic understandings were primarily available through peer-reviewed papers in libraries. Psychological knowledge can now be accessed by anyone with a smartphone. It is concerning that individuals are using information from these sources to self-diagnose.[19,20]

The status of expert knowledge is further challenged by variations in expressions of human distress across cultures, with psychosomatic phenomena subjected to these cultural differences.[21-24] These differences present a challenge to claims of universal psychological truths.[25] The view taken in this article is that cross-cultural awareness is valuable while recognizing that concerns about relativism are valid.[26]

A slip into relativist thinking would be unhelpful, and psychological understandings are more than just a range of different opinions. It is argued here that there are aspects of the human condition that we all share. This has been referred to as a "universal culture" in the sense that there are many human experiences that everyone will live through.[27] Each person will find themselves placed within a particular intersectional locus, situated in varying cultural worlds. However, we can understand their specific way of being in relation to the shared "givens of human existence."[28] The idea of a universal culture is useful because psychosomatic conditions can be approached and formulated within these shared understandings.

The human capacity for empathy is relevant here, especially where there is a need to understand what is happening in another person's life and how they are responding. The word "empathy" entered the English language over a 100 years ago as a translation of the German psychological term "*Einfühlung*."[29] Within this area of psychological understanding, empathy is considered possible even when there are differences in cultural background.[27,30] It is possible that a form of understanding can be attained in which the perceived separation between mind and body is overcome. This article is supported by a review of literature that explores "empathy in research into psychosomatic conditions," using a framework described by Stein.[31]

2. Materials and methods

A search was conducted through Google Scholar and the Open University database, using the terms: "Edith" + "Stein" + "empathy." Over 2,000 documents were identified and screened for those addressing psychosocial phenomena within the contexts in which they emerge. A total of 42 papers were reviewed. The material was found to be complex, suggesting a need to consider it within a broader horizon of changing philosophical positions.

3. Results

The following is an account of how understandings of psychosomatic phenomena are framed across the spheres of biological symptoms, psychological diagnoses, and identity.[32,33] Rather than limiting our understanding to any one of these spheres, this account presents an approach in which the lived experience of psychosomatic conditions can be understood within a more comprehensive philosophical framework. This review begins by exploring the examples of gendered identity and neurodivergent conditions while introducing the concept of epistemic injustice. It then provides an account of a new paradigm in psychological research, including the example of recovery philosophy, in which new research frameworks are accommodated.

3.1. The example of gender identities

In terms of the distinction made between biology and psychology, the notion of gender provides a useful illustration. At a biological level, most people are embodied in a way that can be classified neatly as male or female. At a cultural level, however, there are numerous positions regarding how genders are constructed and performed.

In some cultures, it is only possible to be either female or male, and this requirement can be extremely problematic for individuals who struggle to conform psychologically to a limited, culturally defined gender identity. In such cases, "identity politics" becomes a source of conflict.[34] Psychological researchers are reminded by the ethical guidance of the APA[11] that individuals have a right to express their gender identities. This raises the question of whether researchers should include two or more gender identity options in their assessment forms. If they are employing empathy in their research, this becomes more than a technical question about categorization. Cross-cultural awareness and sensitivity are important.[35]

Health problems and disabilities, such as gender, have a cultural aspect. They are performed and judged in terms of cultural expectations around what it means to be ill or disabled.[21-24] This is why psychological researchers are encouraged to situate their research within the context in which it is conducted and to examine their own motivations. Psychologists may be asked to judge whether someone is expressing their distress in a manner that aligns with a culturally specific definition of a psychosomatic

condition. This task can become entangled with moral judgments about whether a person's suffering is genuine, or who is responsible for addressing that suffering.

The use of empathy in exploring the research participant's lived experiences might enable psychological dispositions to be described in terms that are separate from culturally located identity politics. Unfortunately, it is uncertain whether this is possible.[32,36] We cannot be sure that a person's psychological nature, or "self," exists independently of their cultural context. A psychosomatic condition will be experienced in a way that is specific to that context.[37] It has long been recognized that in some cultures, people are more likely to express psychological distress through physical symptoms,[23] because "idioms of distress" vary.[38] However, this does not mean that psychosomatic conditions are more prevalent in those cultures.[24]

It may occur that practitioners, without reflection, promote the assumptions and values with which they were raised.[39] This means that when working across cultural divides, it is necessary for them to adopt a humble stance, one that involves questioning and suspending narrow views to access a broader horizon.[40] However, when making psychological formulations, there is no position outside of our varying cultural worldviews from which to establish a truly neutral or impartial stance.[16]

3.2. Epistemic injustice

Epistemic injustice occurs when members of a majority group adopt broad, stereotypical definitions of "otherness."[41-43] A member of a minority group then encounters barriers,[44] which are likely to be enforced through multiple microaggressions.[45] When these microaggressions constitute a systematic distortion or misrepresentation of a person's experiences, that person is excluded and silenced. Furthermore, when communications propagate oppressive social narratives, the potential contributions of minority members are denied, resulting in a gross undervaluing of their status and standing. Unwarranted distrust can develop in the absence of shared understanding.[42] In some societies, minority groups have made progress in challenging this form of injustice. In response, psychological researchers have begun to adopt a more empathetic stance.[46]

A shift in the exercise of power can be observed in economically successful nations. While professional expertise was once highly valued, certain social changes have led to a devaluing of scientific knowledge.[17] In these nations, people increasingly claim the right to express their own views. Many now speak of "my truth," with the expectation that their worldview be respected as just as valid as anyone else's.[17] A common slogan from the disability rights movement is particularly informative; "Nothing about me without me." This expresses a demand to be involved, to be consulted on how one is understood and how one's needs are to be addressed. However, the experience of "minority stress" persists,[47,48] whereby individuals must remain constantly vigilant in anticipation of potential stigma and discrimination.

With awareness of problems, such as epistemological injustice[41] and minority stress,[47,48] psychological researchers are turning more often to empathy-based approaches in phenomenological methodologies. Rather than proposing and testing models constructed solely from their own theoretical understandings, they gather lived experiences through dialogue with people who are suffering. Researchers do not presume to have direct access to the nature of a psychosomatic condition. Instead, they invite those who suffer from such conditions to explore and explain their own experiences.

3.3. The example of neurodivergent conditions

The concept of neurodivergent conditions is often traced to the work of Singer.[49] It is noteworthy, however, that the term and related theories have multiple origins before Singer's thesis; these origins can be found in debates involving individuals who themselves have been diagnosed with neurodivergent conditions.[50] In our understanding of these conditions, it is not believed that psychological problems cause bodily symptoms. However, it is known that stress can be an exacerbating factor.[51] These conditions also meet the definition of psychosomatic to some extent, as they are diagnosed through psychological rather than medical assessment. In addition, post-traumatic stress disorder has been conceptualized by a minority of theorists as an acquired neurodivergent condition, in which bodily symptoms are believed to have a psychological cause.[51] It is rarely possible to identify neurodivergent conditions through observable organic causes, although some forms of acquired neurodiversity are exceptions to that rule.

There are conflicting accounts in the existing theoretical taxonomies, with disagreements over which conditions fall within the neurodivergent category.[52] It is also uncertain whether these conditions are neatly divided, fall within clusters, or are spread across spectrums.[52] Where theorists fail to bring certainty, individuals who believe they suffer from these conditions are coming together to develop shared understandings of their own.[51,53] This has led to claims that psychological experts are not qualified to diagnose such conditions because they lack lived experience, raising questions about their capacity for empathetic understanding.[54-56] Some theorists have

described fetal alcohol spectrum disorder as a neurodiverse condition, but this diagnosis is expert-based, imposed, and potentially discriminatory.[57] However, the scientific focus is shifting away from the expert deciding "what is wrong with the person," toward questions of how those who are struggling can understand themselves, and how they can be supported in leading meaningful lives.[44]

Neurodivergent conditions are also experienced differently across cultures. For example, Atherton *et al.*[58] drew contrasts between Japanese and Western societies, showing that a neurodivergent condition may be more commonly identified in certain cultural contexts.[58] Moreover, the ways in which identities are shaped once the condition is identified differ significantly. In Western societies, receiving a diagnosis can be beneficial because it provides access to additional educational resources. In addition, identity politics have evolved to reduce the stigma associated with neurodiverse conditions, an evolution that has not progressed as far in Japan.[58] In one setting, a person may feel distressed upon receiving a diagnosis and resist the label due to negative social consequences, while in another setting, a person may be distressed if they are denied the diagnosis they are seeking.[58]

Overall, when psychological researchers investigate psychosomatic conditions with attention to lived experience, they are increasingly recognizing cultural differences. Within this complexity, it is acknowledged that theorists are struggling to define what it means to have a self that is fixed, fixed in the sense of existing separately from any specific cultural context, and unrelated to locally constructed social identities.[36] It is also recognized that psychosomatic conditions are difficult to describe, understand, or manage independently of those cultural contexts and social identities.[37] Following these conceptual shifts, any psychologist who claims certainty about the nature of another person's self or psychological state is cast into sharp relief. Most practitioners now adopt a more empathetic approach, exploring what is happening, rather than making pre-mature judgments.

From the perspective of culturally sensitive and inclusive research approaches, narrow cultural interpretations are increasingly questioned within a new paradigm.[22,23] Yet, broadly speaking, there remain areas of psychological research where practitioners continue to hold fixed certainties, for example, in educational and disability assessments and forensic settings. Conceptual changes, emerging philosophical positions, and evolving ethical standards present challenges for practitioners who are reluctant to move beyond those certainties. A brief sketch of a developing paradigm in psychological research is outlined below. This is followed by a discussion of how we might begin to establish what is happening psychologically for another person—understandings that can, in turn, help those who are struggling with the implications of this paradigm shift.

4. A new paradigm

Shifts are observed in the philosophies that underpin psychological understandings of human distress.[59,60] With a more rigorous epistemological stance, researchers have explored the contexts within which psychological distress is likely to emerge. Psychological distress is experienced more often by people living in challenging circumstances. These are contexts in which they encounter abuse, discrimination, and exclusion.[39,59,60] It then becomes difficult to confine theoretical understandings strictly within the sphere of psychology. These debates have coincided with social movements in which people have campaigned for inclusion, safety, and improved quality of life.[46] Stress is identified as a contributing factor in the development of many psychosomatic conditions, particularly post-traumatic stress disorder, which can result from interpersonal abuse and conflict.[51]

It has been found that within the profession of psychology, there is a history of discrimination, and members of minority groups have often been excluded or marginalized.[61] In the past, psychological researchers were, as a group, almost exclusively white, male, heterosexual, and drawn from economically advantaged classes.[39] Elements of psychological research are rooted in societies where imperial ambitions were fostered.[39] As a result, psychological theorists have contributed to processes of "othering," pathologizing difference. In positioning others as "psychologically flawed," theorists have targeted groups differing in gender, sexuality, ethnicity, neurotype, religion, culture, embodiment, age, and other dimensions. Psychological theorists have promoted narrow definitions of what is considered "normal" in human behavior,[25,39,62] thereby justifying exclusions, enforcing assimilation, and policing behaviours.[63]

For decades, minority groups have engaged in numerous campaigns and have pushed through important changes. Some barriers to inclusion have been dismantled, particularly where psychological modeling and professional practice were previously part of the problem. One outcome is that, in many societies, the gender balance within the psychological professions has shifted from predominantly male to predominantly female.[64] However, men still make up the majority in higher-paid roles at the top of the profession. It also remains the case that only those from privileged backgrounds can typically afford to pay for the required professional training.

A move toward inclusivity in psychological research comes with a broadening of its theoretical basis. An adaptive example of this move can be found in recovery philosophy.[65] While the theoretical position of most mental health professionals had previously aligned with the medical model, there has been a shift toward an approach more akin to an understanding of disability. Recovery philosophy suggests that symptom reduction should not be the priority.[65] It is more important to help a person adapt and recover a meaningful life.[44] This, again, is a way of working that aligns with social change movements and requires an empathetic stance toward suffering. When knowledge is constructed within this philosophy, it is lived experience that is valued, and peer workers who are "experts by experience" are often employed.[65]

The shift explored in recovery philosophy moves away from the question of "what is wrong with a person," toward an understanding of why people may experience difficulties in living. Across the world, sustainable farming and hunting practices have been marginalized and undermined, as resources are stripped to support industrialized urban living.[66] This is not to romanticize lives that were often challenging and short. These economic developments are relevant to psychological well-being, as millions have migrated because living sustainably was no longer possible. In many societies, they form an underclass, experiencing poor living conditions and providing cheap labor. Across experiences of cross-generational trauma, people have been stripped of their cultural heritage, languages, and community identities. Even without these challenges, stress is commonly experienced simply in moving between cultures.[67]

Industrialization and globalized trade are clearly bringing many benefits, but they are also a cause of suffering. This suffering can be interpreted as a rise in mental health problems, as reported by the World Health Organization.[68] In recovery philosophy, however, good mental health is understood to depend on having one's needs met through a sustainable form of purposeful living within a supportive community setting.[65] This philosophy accommodates a broader and more compassionate understanding of human suffering.

It is useful to note that when people engage in identity politics in relation to migrant populations, the outcomes can be dramatic and distressing. A person's status may be politically disputed, with competing definitions, such as tourist, economic migrant, illegal alien, or even spy. The important point to capture here is that these identities are not psychological in nature. It is a person's geographical location that enables the imposition of such identities. A person's psychological disposition does not change simply because they have crossed a line on a map. However, the meanings imposed through identity politics can have a profoundly negative impact on a person's psychological well-being.

The relevance of recovery work can be supported by emerging empathetic theoretical thinking, particularly within a philosophy known as post-colonial theory.[39] This academic discipline explores the consequences of practices, such as violence, exploitation, enslavement, and forced transportation – practices through which suffering has been imposed on populations globally. Mental health problems, when viewed through this lens, can be understood as natural responses to the circumstances in which people find themselves. As awareness grows, it becomes possible to formulate human distress in a more productive and empathetic manner.

5. Discussion

In their psychological assessments, practitioners have often measured the person as if they possessed only the dimensions of a static and passive object.[12] A battery of tests and questionaries would typically be used, and these would have been tested for validity, a process in which diversity and cultural differences are often treated as problematic. However, we now know that when psychologists apply these procedures, a wide range of variations in the human condition is revealed. For example, psychological screening tools identify various character traits, neurodivergent conditions, mental health problems, and different levels of cognitive functioning. Yet, as psychologists move from treating people as subjects toward engaging them as participants, further dimensions of human existence are uncovered.

When psychologists engage empathetically with participants, they begin to reveal the dimension of human agency. The person is then understood as an actor situated within a social and moral context.[6,37] It becomes evident that individuals face dilemmas regarding how they will be perceived within the identity politics of their cultural settings. There is also the temporal dimension, in which a person attempts to learn from their past, make better choices, and navigate their way toward a preferred future. Their way of being can thus be approached not as a pre-given psychological disposition, but as an adaptive response to their circumstances in the world.

With the conceptual shifts occurring in psychological research, there are increasing calls for humility and the adoption of empathetic approaches.[21,22,69] Empathy is a term often used loosely and commonly associated with feeling something in relation to another person. However, in its original context, the term derives from a

tradition of phenomenological research – an approach that explores the nature of what is given through experience. In phenomenological theory, empathy is the process by which we encounter entities and beings in our world.[70] Stein's[31] account of those processes has inspired a renewed scholarly interest.[71-75]

In Stein's original formulation of empathy,[31] she distinguished between the primordial present, in which we are directly aware of our circumstances with some degree of certainty, and the non-primordial realms of the past and the future. We extend ourselves into these two non-primordial realms through memory, imagination, and anticipation. Under the guidance of Edmund Husserl, Stein developed an understanding of empathy as a process of taking sensory information and filling it out into the experience of a phenomenon. We do not simply receive a fragmented series of signals from our various senses; rather, the whole given quality of the phenomenon is present for us.

In phenomenological theory, it is observed that our consciousness is always directed toward something.[70] We have some control over this, and when things are going well, the difficulties we might encounter in the future can appear vague and diffuse. However, through an empathetic connection with our future self, our anticipations can bring a potential challenge into sharp focus. This is part of our temporality, the way we are always orientated to the unfolding of time, and through it, we extend ourselves into possible future selves. Existence then inevitably causes us to feel anxiety in the face of uncertain futures.

Stein[31] explained that we extend ourselves in a similar way into the being of other people. She proposed different levels of empathy that we may or may not accomplish. For Stein, empathy begins with an emotional feeling, a feeling one's way into the state of being of another.[31] However, she observed that this usually progresses into a turning toward what is happening for the other person. Our feelings are then just as much a response to an imagined sense of how it would be for us if those things were happening in our lives. For Stein, this is not a completely empathetic move. There is a further need to turn again, to truly face the other person, to see how they are experiencing their situation and how they are anticipating their future.[76]

In its fullest sense, empathy for another person, as described by Stein,[31] can only occur through a conversational encounter. Both parties must be willing to open themselves to the nature of the other's experiences. Encounters of this kind reveal both similarities and differences, in what each party experiences, in what has happened to them, and in the future events they anticipate. When we understand another person, we grasp the difficulties and dilemmas they face. This applies equally to their experience of illness.[7,77] We may feel concern for them, but we also recognize that they are the ones who must take responsibility for navigating their way into the future. We may be able to help, but we cannot "fix" them or take their burden from them.

In an empathetic encounter, a psychological researcher is not reduced to an emotionless technician. Their intervention is more than simply following a pre-established procedure to define the state of a human subject. It is argued here that human experiences can only be understood by a fellow human who is willing to be present in all their own humanity. In this understanding, we do not begin as separate individuals. We are enmeshed in a shared embodied existence, an existence in which we trigger bodily responses in each other.[74] It is then necessary that a separation is accomplished, in a recognition that we are moving toward different potential futures, most often holding differing values and desires.

In an existential understanding of our temporality, we are not thought to be fixed in our nature. In a genuine encounter with another person, our empathetic connection can reveal new understandings. There is the possibility of reiterated empathy,[31,71] in which we catch a glimpse of ourselves as seen by the other. Our views, the principles we live by, and our way of being can be transformed through an encounter with another person. In this understanding, we are always changing and becoming.

Phenomenological research remains a minority approach within the discipline of psychology, where quantitative methods still predominate. However, the existential realities addressed by these approaches are known at some level by all people. The understandings associated with existential philosophy are based on the givens of existence, givens that we all encounter across different cultural settings and in our varying embodiments.[29]

With the shift in psychological research toward more inclusive approaches, it is important to consult with those who have psychosomatic conditions. In any research conducted into their way of being, it is increasingly required that people are supported as co-researchers. Empathy and mutual support play a role in this kind of research. It is a kind of research that asks about the nature of a person's existence. Questions are framed in terms of how they are navigating their cultural context, in the unfolding of time, while facing dilemmas and barriers: how identity politics are at play in their world, how they manage their encounters with others, and what meanings they assign to these experiences.

6. The difficulty of adapting to a new paradigm

Within this new way of conducting research, care is needed in psychometric testing. It is important to ensure that a diagnosis is helpful to the person who receives it. A diagnosis can be experienced as a political move that disenfranchises and oppresses them.[7,78] For example, it is proposed within the modeling of psychometrics that some people are narcissistic and lack empathy for others. It is paradoxical if there is no attempt to use empathy in this form of psychological screening. The paradox lies in the observation that it is a narcissistic tendency to label other people as narcissistic. People who are not adequately trained in psychological assessment regularly diagnose each other as narcissists, a form of othering in identity politics, in their social media narratives.[79]

In common understanding, narcissists are people who treat others as objects. They fail to engage empathetically with the experience of others. Instead, they use others to meet their own needs, while defining them within the limited frameworks of their own understandings.[80] It is important to recognize and avoid the paradoxes associated with these interpersonal rhetorical moves. In a more empathetic understanding, a person's need to feel in control could make sense if they live in chaotic circumstances where they lack power. A grasping hold of a sense of certainty and control would then be understandable.

We should, however, be concerned for colleagues who are unreflective, if they continue to take a naïve realist position with certainty, even as they might find themselves in the minority. It would be unhelpful to replicate patterns of epistemic injustice by defining these people with broad stereotypical understandings. It would be appropriate, within a new paradigm, to involve them and seek to understand what is happening. It seems likely that they are under pressure from employers and governmental institutions. In some work settings, narrow cultural beliefs about who is deserving of help and who is not may prevail. Psychologists can find themselves under pressure to make these moral judgments.

Taking an empathetic stance, we would observe that it must be challenging to find that the world is changing and that one's certainties are being questioned. However, it is important to remember how past certainties in psychological theories have caused much damage and human suffering.[39] From the perspective of a new paradigm, these certainties could be thought of as "delusions of colonialism." Those who continue to cling to them can find themselves positioned as oppressors.

From the outside, it might appear that people who maintain naïve realism in their psychological research are experiencing a sense of entitlement. It might seem that they believe that they are the only ones qualified and experienced enough to make judgments about the state of being of others. However, if we slip into making those assumptions about them, we would then be joining them in the stance they have taken.

7. Conclusion

Key points to take from this exploration include the following: there are new expectations regarding how psychological knowledge is constructed. The stance of treating people as measurable objects is questioned. There is a greater awareness of cultural differences and identity politics in a person's experience of who they are. Psychologists are moving away from assessments that define and fix people within pre-established theoretical models. Instead, psychologists are open to treating people as participants in research, valuing their contributions, and paying attention to their lived experiences.

Empathy, as understood within the tradition of phenomenological theory and research, is increasingly recognized as an important aspect of psychological research.[81] Stein's[31] account of those processes has inspired a revival of interest.[71-75] There is an increasing awareness that if someone meets the criteria for a known psychological condition, this is partly an outcome of their circumstances and the cultural meanings of the life context in which they find themselves.[21-25] Rather than describing fixed psychological states, researchers are conceptualizing a person's way of being as an adaptive move; their best attempt at finding a way forward in life. Phenomenological approaches in psychological research can retain the rigor of a scientific framework and thereby overcome the mind/body split inherent in some cultural contexts. People vary in their biopsychological states, but these states manifest differently across cultures.[58] Some states might not appear as often in a specific culture, and cultures vary significantly in the attitudes expressed when they do.

8. Future research directions

This review is tentative, an attempt to capture the degree to which a new awareness of cultural differences is unfolding in psychosomatic health difficulties. It has attended to changes in ethical guidance and philosophical positions, along with the impact of associated social movements. Therefore, there are significant limitations to what can be claimed as established changes in practice. It is only possible to provide some examples of good practice. Further research is needed to explore the challenges psychologists face in complying with contemporary ethical standards and social change and to promote the use of phenomenological research where appropriate.

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REVIEW ARTICLE

Memory impairments in depression

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Abstract

Depression is characterized by persistent depressed mood, loss of interest or pleasure in previously enjoyable activities, recurrent thoughts of death, and physical and cognitive symptoms. Godlewska and Harmer's cognitive neuropsychological theory posits that cognitive dysfunction constitutes a core pathophysiological feature of depression, manifested through negative cognitive bias, memory impairment, and executive dysfunction. Prior studies showed that depression impairs memory, correlating with the severity of depressive symptoms. The hippocampus and cortex critically mediate memory encoding, retrieval, activation, and consolidation. Neurally, depression involves reduced hippocampal activation, prefrontal executive control dysfunction, hypoactivity in emotion-regulating regions, diminished cingulate gyrus activity and connectivity, and amygdala abnormalities. Memory impairment is linked not only to depression but also to systemic inflammation from physical diseases, which may disrupt central nervous system function and contribute to cognitive deficits. To elucidate memory impairment mechanisms in depression and guide precision therapies for cognitive rehabilitation, in this review, we introduce the psychological model and measurement tasks of memory and discuss different types of memory impairment in depression.

Keywords: Memory; Impairment; Depression; Somatic diseases; Hippocampus

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1. Introduction

Depression is a chronic and recurrent psychiatric condition characterized by depressed mood, social isolation, and anhedonia.[1] In addition, depression is a common and burdensome severe mental disorder, which is expected to become the leading cause of disease burden worldwide.[2,3] People with depression suffer from a decline in quality of life due to the disorder itself as well as related medical comorbidities, social factors, and impaired functional outcomes.[4] In 2021, Godlewska and Harmer[5] expanded and refined the cognitive neuropsychological model and proposed the cognitive neuropsychological (CNP) theory, which integrates physiological, social, and psychological factors, providing a theoretical framework for the understanding of the delayed onset of antidepressant drug effects. The point of focus for the CNP model is the negative bias in the processing of emotionally salient information in depression.[5] In addition, the CNP theory emphasizes the importance of interaction with the social environment.[6] In addition,

depression is primarily linked to three neurobiological mechanisms: reduced serotonin neurotransmission, the hypothalamic-pituitary-adrenal axis dysfunction, and impaired hippocampal dentate gyrus neurogenesis. Memory impairment is the most prevalent cognitive deficit in both depression patients and animal models.[7] As a pivotal component of the brain's executive control systems, memory function serves as the critical interface between information encoding, storage, and utilization. Through highly integrated hippocampal-prefrontal circuits, it mediates multi-stage information processing through three fundamental mechanisms: dynamic information routing, real-time cognitive control, and adaptive behavioral output.[8-10] Notably, memory circuits functionally interact with limbic emotion-processing networks, and their dysregulation constitutes a core mechanism underlying impaired emotional homeostasis in depression.[11,12] Depressive patients' failure to update negative memories due to hippocampal-prefrontal dysfunction exacerbates rumination, representing both a disease marker and pathogenic mechanism.[13,14] Extensive evidence indicates the hippocampus plays a central role in memory within the brain parenchyma.[10,15] The hippocampus, a two-layered cortical gray matter structure derived from the entorhinal fold, comprises dorsal and ventral subdivisions. Positioned caudal to the amygdala, its dorsal region mediates spatial memory while the ventral portion primarily processes affective information. The seminal case of Henry Molaison, who developed memory deficits after bilateral hippocampal resection, first conclusively linked the hippocampus to memory, prompting research into memory formation.[16]

Memory refers to the cognitive process in which the brain encodes, stores, and retrieves information about objective matters, including memorization, retention, recall, and recognition. According to the duration of memory, it can be classified into transient memory, short-term memory, working memory, and long-term memory. Instantaneous memory differs from long-term memory, which divides into explicit memory encompassing episodic, semantic, autobiographical memory, and implicit memory. Memory deficits in rodent depression models mirror human depression pathology: impaired spatial memory (reduced Morris water maze performance) and episodic memory (object recognition deficits) reflect hippocampal-dependent dysfunction, while working memory (T-maze) and fear extinction deficits align with prefrontal-amygdala circuit disruptions.[17] Clinical evidence indicates persistent memory impairment across both acute and remissive phases of depression, with cumulative deterioration following recurrent episodes. These cognitive deficits significantly compromise patients' quality of life and may lead to psychosocial disability. A meta-analysis of n-back task performance reveals that while individuals with depression show preserved basic attention, they exhibit specific deficits in higher-order working memory components (updating, maintenance, retrieval) under increasing cognitive load.[18] A neuroimaging narrative review further supports this finding, suggesting that cognitive biases in depression may stem from central executive dysfunction affecting working memory processing, which is linked to persistent negative thinking and rumination, key neural substrates include the left dorsal anterior cingulate cortex, left dorsolateral prefrontal cortex (dlPFC), and default mode network regions.[19] The memory system serves as a central hub in the pathophysiology of depression, rather than a mere epiphenomenon, where the exhaustion of compensatory capacity in memory-related neural circuits triggers acute depressive episodes. Specifically, memory systems drive depression pathogenesis through maladaptive plasticity in the hippocampal-prefrontal-amygdala circuitry, manifested by synaptic pruning abnormalities and reduced neurogenesis.[20] Therefore, this review aims to integrate multiple dimensions of memory impairment in depression, summarize the connections and interactions between depression and memory impairment, provide a basis for in-depth understanding of the pathophysiological mechanism of depression, and offer a new perspective for understanding the social functions and clinical significance caused by memory impairment in depression.

2. Measurement and classification of memory

2.1. Long-term memory

Long-term memory, characterized by its enduring retention and unlimited capacity, forms the foundation for accumulating personal experiences, developing cognitive abilities, and shaping overall psychological growth.[21] Long-term memory encompasses extensive knowledge, a broad scope, and prolonged duration.[22] As a core brain function, long-term memory underpins all cognitive processes with its unlimited capacity, enabling lifelong retention of early experiences. Its representations rely on structural storage spanning hierarchical levels, from conceptual schemas to individual item traces.[23] Neurophysiological studies indicate that the hippocampus and medial temporal lobe mediate long-term memory in healthy individuals, relying on interactions with cortical regions. Low-frequency cortical oscillations and high-frequency hippocampal ripples are essential for this process. An animal study revealed that during spatial and non-spatial memory tasks, hippocampus-cortical network oscillations coordinate to consolidate memories. Notably, such coordination persists even without active memory demands, varying by age, memory intensity, and type.[24] Research shows the

hippocampus is essential for long-term memory storage and retrieval as well as new associative memory formation.[25,26] One study demonstrated that hippocampal-mediated long-range gamma synchronization couples memory engram cells across cortical regions, facilitating memory storage and retrieval. Notably, the experimental mice exhibited prolonged learning duration and slower acquisition rates compared to controls, reflecting severe memory impairment.[27] Behavioral studies using a naturalistic What-Where-When task revealed that depressed patients exhibit situational memory deficits, primarily due to impaired object memory and temporal binding ability compared to controls. These findings confirm the presence of context-dependent memory dysfunction in depression, which co-occurs with heterogeneous long-term memory impairments.[28] Depression selectively disrupts episodic memory, a critical long-term memory system. A meta-analysis demonstrated small to moderate depression-related deficits in episodic memory; deficits were more pronounced in older age, in clinical depression, and in those receiving pharmacological treatment, while fewer deficits were observed in memory for negative material and with higher educational attainment.[29] Depression involves dysregulated neural circuits encompassing the hippocampus, amygdala, and frontal-limbic regions, which are critically engaged in memory processing. Episodic memory encoding, consolidation, and retrieval require phase-synchronized interactions between theta-gamma and sharp wave-ripple (SWR) across hippocampus-prefrontal cortex networks.[30,31] Depression disrupts hippocampus-prefrontal cortex oscillatory coordination, manifesting as attenuated theta phase synchrony, gamma power coherence, theta-gamma phase amplitude coupling, and SWR generation.[32] Dysregulation of monoaminergic and glutamatergic systems in depression directly contributes to domain-specific cognitive deficits. A Danish study found that depressed patients exhibited reduced 5-HT4 receptor binding in the inferior frontal, temporal, parietal, and occipital cortices compared to healthy controls. Untreated patients with moderate-to-severe episodes showed 7.0% lower binding, and verbal memory performance positively correlated with 5-HT4 receptor levels.[33]

An important cause of long-term memory impairment in patients with depression may be chronic stress-induced neuroinflammation. According to clinical evidence, various psychosocial stressors have been proven to accelerate the development of neuroinflammation and mental disorders. Persistent neuroinflammation, in turn, can induce depressive-like behaviors or promote the progression of depression.[10] In a subset of patients, chronic exposure to stress is an etiological risk factor for neuroinflammation and depression. Neuroinflammation affects up to 27% of patients with depression and is associated with a more severe, chronic, and treatment-resistant trajectory.[34] Most of the evidence demonstrating involvement of synaptic and cytoarchitectural/cytostructural changes associated with depression-like behavioral deficits comes from animal stress models, it is well known that chronic stress or chronic corticosterone (main stress hormone of the hypothalamic-pituitary-adrenal axis) administration can induce dendritic reorganization in the prefrontal cortex and hippocampus as well as reduction of the number of synapses.[35] Meta-analyses confirm that inflammation and neural abnormalities are particularly linked to adolescent depression onset in the context of early-life stress.[36,37] In the future, imaging techniques can be further adopted for the assessment of long-term memory in depression to clarify the relevant neural mechanisms, understand the cognitive mechanisms of depression, and develop targeted intervention measures.

2.2. Short-term memory, sensory memory, and working memory

Classical theoretical models suggest that visual short-term memory can be divided into two main memory systems: sensory memory, a short-lasting but high-capacity memory storage; and working memory, a long-lasting but low-capacity memory store.[38] Sensory memory, also known as instantaneous memory, refers to the brief retention of stimuli perceived by sensory organs, typically lasting about 1 s, in a landmark 1960 experiment, based on American psychologist Sperling's concept.[39] Short-term memory is also called short-term storage, primary memory, or active memory. The term indicates different systems of memory involved in retaining pieces of information, or memory chunks, for a relatively short time, typically up to 30 s.[21] Practically, short-term memory functions as a temporary scratchpad for recalling a limited amount of data, typically around 7 ± 2 items, in the verbal domain.[21] Depression involves dysfunction of the dlPFC, a recently discovered brain region that subserves working memory, abstraction, and the thoughtful regulation of attention, action, and emotion.[40] However, the dlPFC is very vulnerable to stress and inflammation, which are etiological and/or exacerbating factors for depression.[40] Neurobiochemical studies have found that depression is associated with abnormal synaptic transmission in the prefrontal cortex, and reduced expression of several synaptic genes has been observed in the prefrontal cortex of patients with depression. Autopsy of individuals who died by suicide after death revealed that the transcriptome sequencing technology (RNA-seq) of the dlPFC tissue also revealed a lower level of gamma-aminobutyric acid type A receptor.[41]

Short-term memory is crucial for higher cognitive functions, yet its storage capacity is severely limited. Thus, it

is necessary to selectively retain information relevant to our goals by controlling attention. This is facilitated by working memory, which consists of short-term storage and executive attention.[42] Working memory is a multicomponent system that is supported by overlapping specialized networks in the brain. Baddeley's working memory model includes four components: the phonological loop, the visuo-spatial sketchpad, the central executive, and the episodic buffer.[43] Working memory serves as a limited-capacity interface between sensory and long-term memory, integrating information from both to support cognitive tasks. Excessive negative emotional information consumes working memory capacity, exacerbating depressive symptoms. Research indicates that individuals with depression are more susceptible to interference from task-irrelevant information, particularly negative emotional stimuli. They struggle not only to prevent its intrusion but also to disengage from it in a timely manner. Consequently, excessive negative emotional information occupies working memory capacity, contributing to the onset and maintenance of depressive symptoms.[44] Depression is associated with deficits in working memory.[45] Several cognitive subprocesses interact to produce working memory, including attention, encoding, maintenance, and manipulation.[19] Studies employing the n-back task in depression reveals impaired processing speed and prolonged response times, though without significant group differences in accuracy, P2 amplitude, or theta event-related synchronization.[46] However, meta-analytic evidence demonstrates pronounced accuracy deficits under higher cognitive loads (peaking at 2-back), with age and clinical severity exacerbating these depression-associated cognitive impairments.[19] Collectively, depressed individuals dedicate greater levels of cortical processing and cognitive resources to achieve comparable working memory performance to controls. In the future, cognitive neuropsychology research could delineate the underlying neural circuits to inform targeted interventions for working memory deficits in depression.

2.3. Autobiographical memory

Autobiographical memory, a universal aspect of human long-term declarative memory, plays a pivotal role in psychological and interpersonal functioning. Growing evidence suggests its frequent involvement in rumination among individuals with depression. Autobiographical memory facilitates the enduring storage of personal life information by integrating both episodic ("I remember" experiences) and semantic ("I know" facts) components. The seamless functioning of autobiographical memory provides a sense of stability to both the self and the external environment, while enabling detailed future planning. Psychologically healthy individuals typically exhibit a positivity bias in autobiographical recall, which may contribute to mental well-being. Impairments in retrieving event-level, specific autobiographical memories, termed overgeneral memory, are recognized as a feature of clinical depression.[47] Poorer autobiographical memory may be a vulnerability for future episodes and improving autobiographical memory specificity could protect against relapse.[48] One well-established framework behind overgeneral memory is the "CaR-FA-X" model. This theory explains overgeneral memory in terms of three interconnected processes: capture and rumination (CaR), functional avoidance (FA), and reduced executive function (X).[49] An updated meta-analysis demonstrates overgeneral and specific autobiographical memory predict the course of depression.[47,50] Notably, a meta-analysis revealed that depression is associated with reduced memory specificity and increased categorical memory retrieval; these deficits were less pronounced in subthreshold and remitted cases, while overgeneral memory was consistently observed across all emotional valences.[51] Autobiographical memory involves the storage and retrieval of information from one's past and ranges from broad life periods down to the minute sensory details of a given event.[52] The successful recollection of events from one's past is critical to identity formation, problem-solving, and future goal direction.

2.4. Prospective memory

Prospective memory is a core neurocognitive ability that refers to memory for future intentions, such as remembering to take medications and to switch off appliances.[53] Any breakdown in prospective memory, therefore, has serious implications for the ability to function independently in everyday life. In many neurological disorders, prospective memory deficits are common even in the earliest stages and typically become more severe with disease progression.[54,55] Results regarding prospective memory function in patients with depression are inconsistent and require systematic investigation. A study utilizing portable functional near-infrared spectroscopy demonstrated that maintaining both social and non-social intentions engages broad activation in the medial and right prefrontal cortex (BA 10).[56] Notably, social intention maintenance specifically enhanced activation in the lateral prefrontal cortex (BA 45/46) compared to non-social conditions, highlighting the pivotal role of prefrontal regions in sustaining intentions and responding to prospective memory cues.[56] Event-based prospective memory refers to the ability to execute delayed intentions upon encountering specific cues; this capacity is impaired in depressed patients and impedes functional recovery, contributing to persistent cognitive deficits during remission.[57] This allows individuals with depression to experience varying degrees of cognitive

impairment during the recovery phase. Depression is associated with multiple neuropsychological deficits, including impairments in executive function, memory, and processing speed, which may hinder daily functioning.

2.5. Interaction between memory and emotion

Affective experiences are commonly represented by either transient emotional reactions to discrete events or longer-term, sustained mood states that are characterized by a more diffuse and global nature. While both have considerable influence in shaping memory, their interaction can produce mood-congruent memory, a psychological phenomenon where emotional memory is biased toward content affectively congruent with a past or present mood.[58] The study of interaction between memory and mood has direct implications for understanding how memory biases form in daily life, as well as debilitating negative memory schemas that contribute to mood disorders such as depression.[59] Hippocampus-dependent cognitive memory and dorsolateral striatum-mediated habit memory represent two distinct memory systems, both modulated by emotional arousal. Emotionally charged events are more likely to be retained than neutral ones.[60] Stressful situations significantly influence memory encoding, especially for emotionally charged stimuli. Theta oscillations, particularly those in the medial temporal lobe, play a pivotal role in this process. Similarly, studies on depressed patients have established a link between amygdala activity and emotional memory. When depressive individuals with impaired emotional memory received brain stimulation to enhance high-frequency amygdala activity, their symptoms showed significant improvement.[61] A magnetic source imaging study revealed that stress enhances memory-related theta oscillations, with particularly pronounced effects observed in the medial temporal and occipito-parietal regions. In addition, theta power increased in response to stress when memories were formed for emotionally negative stimuli instead of neutral ones.[62] This offers fresh perspectives on the brain processes that underlie the connection between stress, emotion, and memory.

3. Somatic disorders and memory

Memory is not only related to various mental illnesses, but it can also be impacted by physical illnesses. Obesity has now reached the status of a global health emergency. Growing evidence indicates that excess body weight correlates with multiple cognitive impairments, as well as structural and functional changes in the brain. Obesity-mediated inflammatory changes affect the physiological functions of the central nervous system, thereby possibly mediating the impact on various cognitive processes.[63] Previous studies have established a correlation between obesity and impairments in the frontal lobe and hippocampus, potentially leading to memory deficits. Empirical evidence further supports this association: a study found that individuals in the obese group had lower cognitive performance in tasks involving planning, decision-making, self-control, and regulation compared with participants of normal weight. This study provides empirical support for the relationship between obesity and cognitive decline, and highlights the potential impact of obesity on cognitive performance in women.[64] Evidence obtained from clinical and experimental studies shows that obesity may be associated with cognitive performance and executive function impairments; and inflammation, oxidative stress, insulin resistance, and hypertension act as mediators for the adverse effects of obesity on the brain.[65] Patients with diabetes mellitus exhibit an increased risk of developing dementia, though the underlying etiology is complex and partially attributable to genetic factors. In individuals with type 2 diabetes mellitus (T2DM), the hippocampus is identified as the most vulnerable brain region.[66] Notably, researchers have identified associations between polygenic risk scores and right hippocampal lymph node properties in T2DM patients, with these lymph node characteristics further correlating with episodic memory performance, demonstrating the existence of a gene-brain-cognition biological pathway.[67] It has been estimated that 20 – 70% of people with diabetes mellitus have cognitive deficits; high blood sugar affects key brain areas involved in learning, memory, and spatial navigation; and the structural complexity of the brain has made it prone to a variety of pathological disorders, including T2DM.[68] Cognitive impairment and subsequent dementia are considered significant health challenges, in patients with established dementia, it is argued that hypertension is the main risk factor for small vessel ischemic disease and additional cortical white matter lesions.[69] Cognitive domains and impairments associated with hypertension include learning, memory, attention, abstract reasoning, mental flexibility, psychomotor skills, and executive function.[70] Stroke survivors may not only face the challenge of physical disability but also the challenge of cognitive consequences. Post-stroke cognitive impairment has been associated with functional dependency and poorer quality of life. It has been found that 60 – 70% of stroke patients have perceptual dysfunction, executive dysfunction, abstract reasoning dysfunction, episodic memory, or language dysfunction.[71] The theory of hemispheric functional specialization refers to the theory that there are differences in the division of labor between the two hemispheres of the human brain (the left brain and the right brain) in cognitive, perceptual, and motor functions. It holds that the left and right hemispheres of the human brain have functional

differentiation and synergy in advanced cognitive functions. This theory predicts that the language working memory of stroke patients in the left hemisphere will be more severely impaired, while the spatial working memory of stroke patients in the right hemisphere will be more impaired.[72] A meta-analysis indicates that the working memory of survivors after stroke is generally impaired. All subsystems of working memory were significantly affected, and similar findings were also reported for non-verbal and verbal tasks. Extensive frontal and parietal network lesions lead to impaired working memory, which in turn results in a reduced ability to maintain both verbal and non-verbal information. Compared with the subacute phase, the effect size in the chronic phase is larger, and most longitudinal studies have shown that the working memory performance of stroke survivors has not improved.[71]

A large amount of clinical evidence shows that patients with concurrent physical diseases not only exhibit disorders in short-term memory encoding and retrieval but also have a significantly increased risk of long-term memory decline and dementia transformation. Future research needs to further clarify the causal pathways and explore the protective potential of intervention measures for underlying diseases (such as blood pressure control and anti-inflammatory treatment) in memory function, with the expectation of providing evidence-based evidence for interdisciplinary comprehensive management.

4. Conclusion

Depressed patients experience severe declines in quality of life due to impaired social and emotional functioning, physical pain, and persistent fatigue. These detrimental effects are further exacerbated by residual cognitive symptoms that endure beyond clinical treatment. This review synthesizes the multifaceted nature of memory impairment in depression from a neurocognitive psychology perspective, examines its potential consequences for social functioning, and discusses the contributions of comorbid physical illnesses to memory dysfunction. These insights deepen our understanding of cognitive health in depression and inform the development of targeted preventive and therapeutic strategies.

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Conflict of interest

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PERSPECTIVE ARTICLE

Letter to the father: Insights into Kafka's understanding of empathy

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Abstract

Letter to the Father is an intimate and revealing classic masterpiece about the complex relationship between Franz Kafka and his father. In this work, he exposed his feelings and thoughts stemming from his daily family and professional life, rooted in the difficult paternal interactions he experienced. The study of empathy, which involves both emotional and cognitive dimensions, can be analyzed through this narrative. The aim of this study is to understand empathy as presented in *Letter to the Father*, with a focus on the cognitive and emotional aspects of this behavior. The specific objectives are to identify the emotional and cognitive aspects of empathy between the characters and to characterize these behaviors in Franz Kafka based on inferences drawn from his writing. This research is exploratory and bibliographic in nature, involving a literature review, reading, logical organization of data, thematic discussion, and writing, with an inductive methodology. It is suggested that this study contributes to a deeper understanding of the relationship between family experiences and the development of emotional and cognitive aspects of empathy while also emphasizing the importance of nurturing welcoming and respectful environments for healthy emotional growth.

Keywords: Empathy; Cognition; Emotion; Literature; Franz Kafka; Letter to the Father

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1. Introduction

The letter written by Franz Kafka (Figure 1) to his father in 1919, when Kafka was 36 years old, was never delivered to the recipient. *Letter to the Father* is an intimate and revealing work that provides a deep insight into the complex relationship between Kafka and his father, Hermann Kafka. In this long letter, the writer exposed his anguish, resentments, and difficulties in communicating with his father, with the power dynamics and apparent apathy of Hermann toward Franz being central themes. These themes allow for an intense analysis of the family dynamics that shaped Kafka's life and his works. The psychological depth of the letter is remarkable, addressing both directly and indirectly the cognitive and emotional aspects of empathy inherent in individual and interpersonal behaviors, revealing the lasting marks and impacts that family relationships have on the individual. Kafka not only described these conflicts but also highlighted important aspects of neuroscience and emotion in the constitution and expression of the subject.[1]

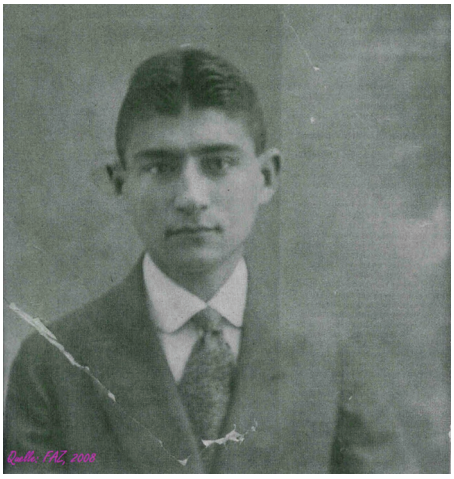

Figure 1. Franz Kafka (July 3, 1883 – June 3, 1924) by Pittigliani, 2005. Licensed under CC BY-NC-ND 2.0. Taken from https://openverse.org/image/dac3b7c3-779c-44af-8087-db4c1b122262?q=franz+kafka&p=15.

The autobiographical bias of Kafka's works, including *Letter to the Father*, appears in other narratives that explore the themes of bureaucracy, maternal absence, loving relationships, and paternal authoritarianism.[2] Kafka found in writing a way to expose his dislikes and sought an absolute expression of his complex and contradictory emotions in response to the authoritarian personality of Hermann.[3] An example of this is the tale *The Verdict*, in which Kafka equated his father with a higher power – one with absolute control over the son and capable of subjecting him to condemnation.[4] Kafka's sense of inferiority to Hermann is also present in the novel *The Metamorphosis*, where he describes a manipulative father who incessantly assumes the role of provider in the family and does not accept a child who does not perform a "worthy" job.[5]

Considering the descriptions of human behavior in Kafka's writing, as well as the fantastic symbolisms rooted in his private experiences, empathy can be identified as an agent of human relations within Kafkaesque literature. Empathy thus becomes essential in conceptualizing interpersonal dynamics. In this sense, understanding empathy requires an analysis of its three aspects: cognition, emotion,[6] and motivation.[7] The cognitive aspect is characterized by the intellectual ability to recognize and understand other's emotions and thoughts, from the perspective of others to oneself,[7] and is particularly susceptible to educational processes over the course of life.[8] The emotional aspect of empathy involves the feelings that arise in the observer when interpreting the emotions of a third party.[6] The motivational aspect can be defined as the internal motivation that generates in an individual the potential to act with empathy.[7]

It is important to note that empathy is a complex and multifaceted phenomenon that permeates human relations and manifests itself in different areas of social life, including the arts and literature. According to Stansfield and Bunce,[9] there are consistent relationships between reading fiction and the effective development of empathy in readers. Their studies indicate that both cognitive improvement and affective empathy are related to literature, with the difference lying in the way they develop. The first is related to the quantity of fiction books an individual reads, while the latter is linked to how emotionally involved the reader feels in the narrative. In general, the number of fiction books read by an individual directly impacts the improvement of cognitive empathy, compared to control groups. Immersion in the work and the level of involvement with the narrative influence affective empathy. Both findings support the notion that the reading habit affects individuals' real empathic abilities.[9]

Letter to the Father appears to bridge literature with the real-life themes of family relationships, which can either promote or inhibit the development of empathy. In general, cognitive empathy and emotional empathy within family relationships significantly contribute to psychological development, making individuals more understanding, emotionally intelligent, socially altruistic, and better equipped to handle relational challenges.[10] Kafka's narrative can thus be interpreted as a testimony to his family experiences and the impacts that this oppressive environment had on his life and works.

Literature acts as a means for personal formation, enabling the experience of diverse situations without directly encountering them, thereby fostering empathy.[11] This idea is supported by the fact that literary narratives simulate or are based on real issues, prompting readers to consider their consequences and impacts, which can lead to subtle changes in the subjects and their perceptions of the world beyond the pages.[12]

Literature provides opportunities for understanding personal and interpersonal relationships, with *Letter to the Father* standing out in this regard. When interpreting this work, empathic skills are included in the list of cognitive and emotional behaviors. Taking these aspects into consideration, a question arises: what are the emotional and cognitive aspects of empathy found in the characters of the narrative, and those that relate solely to Kafka's behavior, as presented in *Letter to the Father*?

The aim of this study is to understand empathy presented in *Letter to the Father*, highlighting the cognitive and emotional aspects of this behavior. The specific objectives are to identify the emotional and cognitive

aspects of empathy in the characters and to characterize these behaviors in Franz Kafka, as inferred from his writing.

2. Materials and methods

This research is exploratory, as it provides an overview, of an approximate nature, of a certain phenomenon, and bibliographic, as it is based on already established material, mainly consisting of books and scientific articles.[13] The methodology involved a bibliographic survey, reading, logical organization of the data, thematic discussion, and writing. The method used was inductive.

Data collection was carried out using the Scielo, Science Direct, and PubMed databases, as well as libraries and websites of various research institutions, universities, and academic and scientific repositories. The associated descriptors included: Empathy and literature; Franz Kafka and emotion and empathy; cognition and empathy; book and behavior; Franz Kafka and *Letter to the Father*; empathy and *Letter to the Father*; empathy and motivation; guilt and Franz Kafka; father and Franz Kafka and power; *Letter to the Father* and fear; hostile environment and development and empathy; fear, and empathy.

Data processing was carried out using the content analysis technique, which involved pre-analysis (bibliographic collection and preliminary reading of the material, logging [exploration of the material in full, organization, and optimization of the reading], and the interpretation of results (establishing relationships between the phases of research). This method allowed for the investigation of the language and underlying meanings in the narratives, in this case, from the reading of *Letter to the Father* by Franz Kafka.

3. Results and discussion

3.1 Emotional and cognitive aspects of empathy in the narrative

This chapter presents situations from the work that refer to empathic skills regarding personal relationships described by Kafka with his family and among family members, as well as with the employees of his father's trade. These situations were examined to discussions about the construct of empathy within the literary framework of Kafka.

From the perspective of the facets of empathy, the analysis of *Letter to the Father* presents emotional and cognitive elements in both personal and relational descriptions by Kafka. The presence or absence of empathy and its characteristics will be discussed in specific situations narrated between the characters, given the complexity of the construct.

The constant experience of oppressive situations can be an obstacle to the development of empathy. In addition to individual factors such as genetics, neural aspects, and temperament, there are socialization factors at play, such as imitation, parental styles, and the relationship between parents and children.[14] For the development of empathetic behavior, it is crucial to attend to contextual variables that involve emotional and cognitive expressions from parents toward their children, as well as parental attitudes within the family. These attitudes can span a wide range of possibilities, including the presence or absence of acceptance, clear education, limits, and expressions of anger or affection.[15]

One of the first perceptions described by Kafka in the narrative is that the father, in a despotic way, despised people under exaggerated pretenses and, above all, always positioned himself in a state of superiority. A parallel can be drawn between the behavior described to the father and the ability to understand other people's experiences, which, according to Zaki and Ochsner,[16] is a fundamental aspect of empathy. The opposition to this capacity for understanding does not exclude the feeling of empathy; it may, in fact, arise as a result of social and/or psychological factors, presupposing neglect and discrimination.[17]

The result of Hermann's feeling of superiority toward his family and other personal relationships manifested in behaviors of isolation and detachment. According to MacDonald and Schermer,[18] the difficulty in establishing emotional connections with other people, as well as the excessive search for validation – as perceived in the narrative through the father's attitude of placing himself above others – can lead to loneliness, often stemming from authoritarian positions. By portraying the father in an emotionally detached way, Kafka seemed to highlight the tragic consequences of these behaviors. The father's desire for power and control transformed into an emotional prison that alienated him from others, including his own children.

In this context, Kafka described his father's aversion to people who are dear to his son, even without knowing them. He disqualified them as if they were bugs or otherwise contemptible,[1] suggesting the father's empathic difficulty in understanding his son's personal bonds. This situation may indicate a harmful dynamic of parental control. In healthy family relationships, the ability to take the perspective of others is a crucial skill for understanding emotions and supporting choices, which contributes positively to the empathetic and emotional development among family members.[19]

In some passages of the narrative, Kafka questioned the methods of education used by his father with his children. Kafka attempted to understand the teachings he received in childhood by comparing them with the situation of

Felix – Hermann's grandson. However, Kafka highlighted that although Hermann is an important figure as the grandfather, his attitude does not cause significant harm to the child. On the other hand, for his own son, the impact was quite distinct, as the father represented everything.[1] In addition, there are excerpts from the work that reference Kafka's sister, Ottla, and their father, in which it is written:

For example, to Ottla, you often say: With this one, you cannot talk about anything: She jumps on the neck immediately, but in reality, she is not the first to do that; you confuse the thing with the person; it is the thing that jumps on your neck and immediately you make a decision about it, without hearing the person; what later is still argued can only irritate him, never convince him.[1]

In this perspective, the father is portrayed by the son as authoritarian and rude, which is especially relevant when taking into account the position he occupies within the family context, being, in this narrative, one of the main educators in the children's lives. According to Kusiak *et al.*,[20] parents who encourage and offer emotional support tend to be the ones best able to put themselves in others' shoes, and, as caregivers, they show greater empathy for their children's feelings. This, in turn, improves interactions between them and facilitates the regulation of their own emotions. In a household where parental education is influenced by a lack of empathic skills, harmful effects on children are presumed, affecting both emotional regulation and interpersonal and family relations.[20]

It is pertinent to note the association of fear that Kafka experienced with his father, triggered by situations he witnessed in his childhood and involving third parties. He stated that, as a boy, he felt anesthetized when hearing swearing in conversations at home, especially in his father's shop.[1] Fear is an emotional state of insecurity about a person, situation, or object whose manifestation is related to the reality in which the subject lives and motivates its expression.[21] For example, fear can be experienced by observing a situation,[22,23] and in this respect, an individual who observes an oppressive situation suffered by another person is able to generate behavioral responses of fear, which are significantly influenced by the presence of the empathic skill.[22]

One can see the emotional state of fear in Kafka's account of his father's trade as a result of both the oppressive and intimidating environment that the store represented, as well as the negative experiences lived in this place. Kafka declared that he was tormented and ashamed to witness the tyrannical treatment dispensed to employees by his father so that no place in the world could have been as bad. He exemplified this by describing the humiliation and disrespect suffered by the employees in the store, such as when his father says, "This sick dog should burst at once," when referring to a salesman with pulmonary disease.[1] The hostile environment established between the employees and Hermann extended into Kafka's professional life and his future. Kafka wrote, "The relationship I established in the shop with my peers went beyond it and reverberated in my future."

The perception of injuries directed at employees was one of the factors that led Kafka to feel dissatisfaction with his father's trade, which can be associated with aspects of emotional empathy, such as the ability to sensitize to and share the affections of others. However, it also indicates a difficulty in establishing limits and distinguishing what belongs to oneself and what belongs to others, leading to emotional overload that brings anguish instead of adequate empathic responsibility.[24] Therefore, Kafka seemed to avoid contexts that refer to experiences with his father, as he did not feel confident or free to develop his own skills and express his behaviors, as inferred from the passage below:

Sometimes I imagine an open world map and you stretched across it. For me, then, it is as if only the regions that you do not cover or that are not within your reach were considered.[1]

The self-image of an individual and the image formed about third parties are developed from experiences in the relationships between the subject and significant figures, particularly caregivers.[25] In Kafka's various writings, elements that highlight his negative self-perception are present, notably stemming from the early and authoritarian influence of his father. This is evidenced by his description of a frequent feeling of nullity that dominated him, arising from this relationship.[1]

Throughout the work, different personalities are narrated and associated with the conduct of the father, one of which is Kafka's mother. From the text, her participation in Kafka's life was portrayed as silent and affectionate, manifested in a character who tried to weigh the actions between father and son. Some excerpts from the letter reveal these aspects, as Kafka referred to his mother as being of unlimited goodness toward him, but he perceived this as connected to his father's influence. In other words, the relationship was not healthy. Moreover, the mother secretly protected him from his father.[1] While the mother presented herself as a mediator in the conflicts that troubled the family and received affection and attention from both her husband and son, she was not sufficiently spared from the troubled relationship between them, receiving blows from both sides.[1]

Kafka portrayed his mother as sensitive to the emotional, physical, and psychological needs of the

children, mitigating the harmful effects of the relationship between other family members. She projected a positive influence on Kafka when compared to Hermann. The behavior exhibited by the mother aligns with empathy, and in this context, it can be understood as having a beneficial influence on the children's development. More empathetic mothers tend to raise children who are also more empathic.[26]

It is pertinent to note the family configuration in which Kafka was raised, specifically within a Jewish tradition. This context is key to understanding the behavior described in the next section. The patriarchal education of this culture granted the father full authority over the lives of the children who lived with him, whether married or not, as well as over his wife.[27] This family model, which restricted behaviors and demanded conformity to tradition, was challenged by new ideas of education and individual autonomy, especially among young urban Jews, who had greater access to secular thinking and emerging nationalism.[28] In this sense, the social and political changes of the 19th century led Jews in central Europe to face pressures from modernization, often conflicting with family traditions,[29] which coincided with Kafka's time.

Kafka's father exemplified the common authoritarian fatherhood of the period. He represented a Jew who had risen economically, breaking from the rabbinic tradition to integrate into the bourgeois world of central Europe.[29] This transition created conflicts within his family, as his children witnessed the influence of two different worlds: The rigidity of traditional parenthood and the intellectual freedom of modern thought.[29]

In Kafka's case, his relationship with his father was marked by a mixture of fear and frustration. *Letter to the Father* highlights the emotional impact that the paternal figure had on the son and reflects the challenges of a young Jew raised in a family trying to balance tradition and modernity. This conflict was manifested, even indirectly, in his literary work, where the figure of the father often appears as a symbol of absolute oppression and judgment.[30]

Reading *Letter to the Father* allowed for the identification of empathetic behaviors in different family situations, especially in the relationship with his father, which extended to his professional interactions. The following section presents and discusses data related to Kafka's own emotional and cognitive behavior based on what can be inferred from the letter addressed to his father.

3.2. Kafka's emotional and cognitive behavior in the narrative

This section aims to examine the different facets of empathy, particularly to Kafka's interactions with the recipient of the letter, his father, as well as understanding the psychological consequences experienced by Franz, which may be directly or indirectly linked to the education imposed by his father.

Kafka's life was notably impacted by a hostile environment in which fear became a dominant emotion, accompanied by constant guilt. This combination prevented him from expressing his individuality, feeling present, or realizing his dreams. According to Araújo and Albertini,[31] traumatic experiences that occur without the necessary psychological structure tend to generate negative feelings, which are then repeated in contexts and relationships unrelated to the original trauma but are nonetheless rooted in prior experiences. As a result, the consequences of Kafka's interpersonal relationships are evident throughout the letter, such as the inconsistency and superficiality of his romantic relationships. This can be observed in the following passage: None of the ladies disappointed me; only I let them down. My judgment of them is exactly the same as when I wanted to marry them.[1]

There are moments in the narrative where Kafka's feelings are externalized through observing and reflecting on his father's behaviors, the relationship between them, and the motivations underlying the father's attitudes, thereby demonstrating the presence of the emotional aspect of empathy in Kafka. This empathic facet is defined, according to Roza and Guimarães,[32] as the emotional response triggered in an individual, resulting from the ability to appropriate emotions experienced by another subject. This can be exemplified in:

I admit that as a child, I had no empathy for this (later I did), and I did not understand how you could somehow expect people to be sorry for you. [.] I only later understood that you were indeed suffering a lot because of your children.[1]

In this fragment, Kafka revealed an effective response to the reality lived by his father, narrating his ability to understand paternal emotions, even if he had not undergone something similar himself. The ability to understand and share emotions is a form of emotional empathy,[33] as evidenced in Kafka's treatment of Hermann. Moreover, Kafka repeatedly demonstrated a desire for a harmonious relationship with his father, as when he wrote: I would have been happy to have him as a friend, boss, uncle, grandfather, even (although more hesitant) as a father-in-law. But just as a father, you were too strong for me.[1]

According to Hoffman,[34] empathy arises not only from shared suffering but also from a genuine desire to connect with others. Kafka's yearning for a connection with his father can be interpreted as a feeling of frustration resulting

from his difficulty in establishing emotional empathy. The letter appears to be an appeal for a closer paternal bond and indicates an implicit search for a different kind of family relationship.

It is true that Kafka's affective understanding is not the only way through which he attempted to approach his father, as his efforts to understand his father's behaviors often involved the cognitive sphere. In this sense, cognitive empathy corresponds to the ability to understand and predict the behaviors of another person based on their mental states,[32] without necessarily experiencing the same emotions.[35] This facet of empathy activates complex cognitive functions of mentalization and perspective-taking, but not emotional sharing.[32]

Kafka's effort to understand his father's motivations for some of his actions is repeated throughout the narrative, as are his attempts to justify Hermann's behaviors – indications of cognitive empathy in the narrator. According to Mansur *et al.*,[36] this form of empathy is characterized by the ability to simulate another person's thoughts and feelings. The following excerpt underscores Kafka's efforts to comprehend his father's reasoning and justify his actions:

The fact that at this point you were mistaken, perhaps due to the circumstance that in reality you did not know anything about my personal relationships, assuming, suspicious, and jealous (do I deny that he likes me?), that I had to make up for my family life because it would be impossible for me to live the same way out there.[1]

In their analysis of the structure of *Letter to the Father*, Deleuze and Guattari[37] explained that Kafka appears in figurative form, writing indirectly on various themes to preserve the real subject. A characteristic element connected to this figurative structure is the incessant search for exoneration. According to Higa,[38] all subjects are continuously absolved throughout the writing process, demonstrating an externalization that nothing is truly resolved. Although the discourse focused on relieving guilt, the theme often suggests that innocence is generalized – yet guilt is equally distributed.[38] This is evident when Kafka wrote: This usual way of seeing things I consider only fair in so far as I also believe that you have no fault for our distance. But I also have not the slightest fault.[1]

At times, Kafka showed compassion for the actions of his father by attempting to recognize his feelings and relieve him of guilt despite the anguish this process of understanding entailed. Kafka explicitly described his pain upon noticing that his father was impressed by apparently superior people and believed he needed superficial affirmations of worth, often bragging about them.[1] In this sense, when one projects the self and its reality onto another occurs, and thereby feels the pain and suffering of that other, the motivational aspect of empathy emerges – an aspect directed toward reducing negative feelings in oneself or in others.[39]

The motivational aspect of empathy is linked to the capacity of individuals to become more inclined toward prosocial behavior – that is, actions intended to promote care and well-being in others.[40] Kafka's motivation for writing the letter can thus be interpreted as a prosocial act aimed at alleviating his own suffering, where he attempted to articulate his conflicts with his father and outlined reasons not to place blame. Kafka was tireless in his pursuit of understanding Hermann's role in the anxieties that permeate his life, seeking a resolution that remains in the realm of ideas. This relentless search for understanding may stem from the need to express the most complex feelings an individual can experience.[7]

Kafka wrote to his father:

Dear father: You recently asked me why I claim to be afraid of you. As usual, I could not answer, partly because of the fear that I have of you, partly because in the motivation of this fear intervened so many details that I could hardly summarize them in a speech. And if I try to answer in writing, it will be, without doubt, very incomplete because, also, when writing, the fear and its consequences inhibit me before you and because the magnitude of the subject far exceeds my memory and my understanding.[1]

This passage appears to reflect Kafka's motivation to express himself in response to his father's attitudes throughout life – an effort to understand him across the varied contexts and ramifications of his behavior. Throughout this process, Kafka demonstrated the motivational empathy he developed throughout his life.

4. Conclusion

The analysis of the emotional and cognitive aspects in the narrative of *Letter to the Father* demonstrated that the authoritarian behavior of Hermann Kafka deeply affected Franz Kafka's life. Kafka's familial environment, in which the father figure was dominant, impacted Kafka's development of empathic abilities, as fear, isolation, and a weakened self-image were constant in his personal and professional relationships. Kafka's difficulty in expressing his feelings to his father – stemming from their separation within an oppressive environment – and his unfulfilled desire to strengthen the paternal bond represented a significant barrier to his individuality.

The manifestation of empathetic behaviors, in both their emotional and cognitive facets, was observed among the characters in the narrative, specifically in Kafka's own

behavior while writing the letter. It is demonstrated that his father, mother, and other significant figures in his life also contributed to the shaping of his empathetic development. The excerpts selected serve as a sample of what can be found in other Kafkaesque works, exploring themes related to the emotional and cognitive expression of empathy that extend into personal, familial, and professional spheres.

Kafka's letter, beyond revealing his personal struggles in relation to his relationship with his father, allows reflection on the complexity of interactions within the family context and the impact of parental practices on the emotional and cognitive development of children and, consequently, on the formation of empathic capacities. It is suggested that this study has contributed to a deeper understanding of the relationship between family experiences and the development of emotional and cognitive aspects of empathy while also emphasizing the importance of welcoming and respectful environments for the healthy emotional growth of the individual.

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PERSPECTIVE ARTICLE

Discovering the mind-heart connection: Thoughts in the mind pass through the heart before influencing the body

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Abstract

Understanding human consciousness has long been a central focus of scholarly inquiry across disciplines. While conventional perspectives often attribute cognition solely to the brain, both ancient wisdom and modern research suggest that the heart also plays an integral role in this complex interplay. This paper explores the hypothesis that thoughts originate in the mind, traverse the heart, and subsequently influence the body. Drawing from ancient philosophical traditions, contemporary neurocardiological insights, and Qur'anic teachings, this research presents a holistic framework of consciousness that bridges the physical and metaphysical realms. By challenging the conventional brain-centric view of consciousness, it proposes an alternative understanding of the thoughts that originate in the mind, pass through the heart, and subsequently influence other parts of the body. Through an examination of historical perspectives, recent neurocardiological studies, and extraordinary medical cases, this study aims to advance a more integrated understanding of human consciousness and behavior.

Keywords: Consciousness; Human behavior; Interdisciplinary philosophy; Mind–heart connection; Neurocardiology; Qur'anic insights

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1. Introduction

The quest to understand human consciousness has long captivated scholars across various disciplines. Traditional scientific perspectives often position the brain as the epicenter of cognition. However, emerging research and ancient wisdom suggest a more nuanced interplay between the mind and heart. This paper explores the hypothesis that thoughts originate in the mind, pass through the heart, and subsequently influence the body. Supported by both Qur'anic teachings and contemporary scientific observations, this exploration aims to present a comprehensive framework that encompasses both the physical and metaphysical dimensions of human existence.[1,2]

In recent scholarly pursuits, I have authored two significant articles exploring the intricacies of the mind–body relationship. The first article, published in the *Journal of Neurology and Translational Neuroscience*, examines the mind–brain relationship. The present perspective article, my most recent contribution, focuses on the mind–heart relationship. These works challenge conventional views by proposing that consciousness

is not localized within the brain but rather exists as a state of the mind intricately linked to metaphysical dimensions. Traditional neuroscience has yet to pinpoint a specific location in the brain where consciousness resides, prompting further investigation into the true nature of consciousness.[3]

Drawing on ancient philosophical insights and divine teachings, this research proposes that consciousness is a state of the mind fundamentally connected to the metaphysical realm. This state transcends physical boundaries and is not confined to a specific locality within the body. The brain and heart, though critical to human function, are not the origins of consciousness, but rather, they serve as tools of the mind. The mind, an immaterial entity, utilizes these organs to interact with and influence the physical body. This insight aligns with the ancient philosophical and divine perspective that, during human creation, God breathed the immaterial essence – the soul – into the material body. This essence, referred to as *Nafs* in classical Arabic, serves as a bridge between the immaterial and material realms.[4-6]

A pivotal finding in my research is the concept of intention as a unique attribute of the mind. The mind employs the body as a tool through its intentions, directing physical actions and behaviors. This dual control mechanism highlights how metaphysical principles govern physical matters. The heart and brain are instrumental in this process, serving as conduits through which the mind manifests its intentions in the physical world. Further emphasizing that consciousness is a state of mind but not a locality, the research suggests that thoughts originate in the mind, pass through the heart, and subsequently influence the brain and other parts of the body.[7,8]

This paper integrates scientific research, philosophical inquiry, and Qur'anic insights to present a comprehensive understanding of the mind–heart connection. By challenging the conventional brain-centric view of consciousness, the study offers a holistic perspective on human nature, emphasizing the heart and brain as tools of the soul (divine essence) or mind. The findings highlight the profound interplay between the physical and metaphysical realms, inviting further exploration into the nature of consciousness and the limits of physical understanding.[9,10]

1.1. Research background

In recent years, studies in neurocardiology have highlighted the heart's role in emotional and cognitive processes, suggesting that the heart may influence the brain more than previously thought. In addition, ancient philosophical traditions and religious teachings, including Qur'anic insights, have long emphasized the heart's significance in human consciousness.[11,12]

1.2. Purpose and significance

This paper explores the hypothesis that thoughts originate in the mind, pass through the heart, and subsequently influence the body. By integrating perspectives from modern science, ancient philosophy, and religious teachings, this study aims to provide a comprehensive framework that encompasses both the physical and metaphysical dimensions of human existence.[13,14]

1.3. The present state of research and challenges

Despite growing interest in the mind–heart connection, significant challenges remain in fully understanding this complex relationship. The present research remains fragmented, highlighting the need for interdisciplinary approaches that bridge the gap between traditional scientific methods and holistic perspectives.[15]

2. Ancient philosophical perspectives on the mind–heart connection

2.1. Greek philosophy

2.1.1. Philosophical contributions of Plato

Plato, a towering figure in Greek philosophy, introduced the concept of dualism, which divides the mind and body into distinct entities.[1] While he did not explicitly attribute cognitive functions to the heart, his work laid the foundation for understanding the mind as an immaterial entity. Plato's ideas complement the hypothesis that the mind influences the heart, which in turn affects the brain. This dualistic approach aligns with the idea that thoughts originate in the immaterial mind and pass through the heart before manifesting in the physical body.

2.1.2. Aristotle's views on the heart

Aristotle, one of the most influential figures in ancient Greek philosophy, believed that the heart was the central organ responsible for sensation and intelligence.[2] He proposed that the heart was the seat of the soul and played a crucial role in the processing of thoughts and emotions.[2] According to Aristotle, the brain functioned primarily as a cooling mechanism for the blood heated by the heart's activity, thereby supporting its function. This perspective placed the heart at the core of human consciousness and perception, in contrast to modern views that localize consciousness solely in the brain. Aristotle's views highlight the heart's integral role in cognition, suggesting that the heart processes thoughts before they reach the brain.

2.2. Egyptian beliefs

2.2.1. Heart in ancient Egyptian culture

In ancient Egyptian culture, the heart was considered the center of life, morality, and intellect.[3] Egyptians believed that the heart contained the soul and was the seat of emotions, thoughts, and conscience. During mummification, the heart was carefully preserved, as it was believed to be essential for judgment in the afterlife. The "weighing of the heart" ceremony depicted in the *Book of the Dead* illustrated this belief, where the heart was weighed against the feather of Ma'at, the goddess of truth and justice. A heart lighter than the feather indicated a virtuous life, allowing the deceased to enter the afterlife. This cultural reverence for the heart highlights its perceived role in cognition and morality, aligning with the hypothesis that thoughts influence the heart first before affecting other parts of the body.

2.3. Chinese medicine and philosophy

2.3.1. The heart as the emperor

In traditional Chinese medicine and philosophy, the heart is viewed as the "emperor" of the body, governing the mind and spirit.[4] It houses the *Shen*, which translates to "spirit" or "mind," and is responsible for consciousness, thought processes, and emotional well-being. The *Shen* integrates and controls mental functions, maintaining harmony between the body and mind. This perspective supports the idea that the heart plays a central role in processing thoughts and emotions, influencing overall health and behavior. The heart's primacy in Chinese philosophy aligns with the view that thoughts pass through the heart before affecting the brain and body.

2.4. Indian philosophy

2.4.1. Atman and the heart

In Indian philosophy, particularly in the Upanishads, the heart is depicted as the seat of the *Atman*, or the inner self.[5] The *Atman* represents consciousness and self-awareness, residing within the heart. This view supports the idea that the heart is central to one's true nature and consciousness, influencing the mind and body. The heart *chakra* (energy center), known as *Anahata* in yogic traditions, is considered the center of compassion, love, and emotional well-being, further emphasizing its integral role in human experience.

2.4.2. The Anahata chakra

The heart *chakra*, or *Anahata* in yogic traditions, is the fourth primary *chakra* and is associated with love, compassion, and emotional balance.[6] It is believed to be the center of emotional intelligence and connection, facilitating the flow of energy between the physical and spiritual realms. Practices such as heart-centered meditation aim to align the heart with the mind, suggesting that the heart plays a pivotal role in accessing deeper states of consciousness and intuitive knowledge.

3. Scientific perspectives on consciousness and the heart

3.1. Neurocardiology and the heart's role

3.1.1. Heart-brain interaction

Neurocardiology is an emerging field that explores the complex interactions between the heart and the brain.[1] Research has shown that the heart is not merely a passive organ but actively communicates with the brain through neurological pathways, biochemical signals, and electromagnetic fields.[2] The heart contains a complex network of neurons that enable it to act as a mini-brain, influencing emotional and cognitive processes.[3] This network, often referred to as the "heart–brain," has the capacity to process information, learn, remember, and even make decisions independently of the cerebral cortex.[4]

3.1.2. The heart as an information processor

Studies conducted by the HeartMath Institute suggest that the heart plays a crucial role in processing emotional and cognitive information.[5] The heart's rhythmic patterns can directly affect brain functions, influencing emotional experiences and cognitive processes.[6] The heart sends more signals to the brain than the brain sends to the heart, and these signals can influence perception, emotional processing, and higher cognitive functions.[7]

3.2. Brain-heart communication

3.2.1. Autonomic nervous system (ANS)

The ANS plays a vital role in regulating the communication between the heart and the brain.[8] It comprises the sympathetic and parasympathetic nervous systems, which manage the body's stress response and relaxation state, respectively.[9] The vagus nerve, a major component of the parasympathetic nervous system, acts as a primary conduit for heart-brain communication.[10] It helps regulate heart rate, blood pressure, and other physiological functions by transmitting signals between the heart and brain.[11]

3.2.2. Heart rate variability (HRV)

HRV is a measure of the variation in time between each heartbeat, and it is considered a key indicator of the body's ANS function.[12] High HRV is associated with improved emotional resilience, cognitive flexibility, and overall well-being.[13] Studies have shown that HRV reflects the heart's

ability to respond to various emotional and physiological stimuli, indicating a close link between heart rhythms and mental states.[14]

3.3. Electromagnetic fields of the heart

3.3.1. HeartMath Institute's research

The HeartMath Institute has conducted extensive research on the heart's electromagnetic field and its impact on human physiology and psychology.[15] The heart generates an electromagnetic field that is detectable several feet away from the body.[16] This field is the most powerful rhythmic field produced by the human body and can influence emotional states, stress levels, and overall health.

3.3.2. Impact on social interactions

The heart's electromagnetic field can affect not only our own emotional states but also those of people around us.[16] Research suggests that the heart's electromagnetic field can synchronize with the fields of others, creating a form of energetic communication that influences social interactions and relationships.[16] This phenomenon, known as heart coherence, highlights the heart's role in fostering emotional connections and empathy.[16]

4. The role of the heart in emotions and physical health

4.1. Emotional states and heart rhythms

The heart's response to emotional and mental states is a fascinating interplay of physiological and psychological factors. Different types of heartbeats are triggered by various thoughts and emotions, with each influencing hormone production and glandular secretion.[1-3]

4.1.1. Types of heartbeats

(i) Normal heartbeat (resting heart rate): A steady, regular rhythm maintained during rest, with an average rate of 60 – 100 beats/min (bpm) for adults. This type of heartbeat reflects a calm and relaxed state, with balanced hormonal secretion.

(ii) Elevated heartbeat (tachycardia): An increased heart rate, typically above 100 bpm. This can be triggered by emotions such as fear, happiness, and stress:
   (a) Fear: Part of the fight-or-flight response, fear elevates the heart rate through the release of adrenaline (epinephrine) from the adrenal glands.[4,5]
   (b) Happiness: Joy and excitement can elevate the heart rate due to the release of endorphins and dopamine.[6]
   (c) Stress/anxiety: High levels of stress or anxiety can lead to a persistent elevation in heart rate, accompanied by increased levels of cortisol and adrenaline.[7]

(iii) Decreased heartbeat (bradycardia): A slower-than-normal heart rate, typically below 60 bpm, which may occur during deep relaxation or meditation. This state promotes the release of calming hormones such as serotonin and endorphins.[8]

(iv) Irregular heartbeat (arrhythmia): An abnormal rhythm, which can include skipped beats, extra beats, or an irregular pace. This can be triggered by emotions such as depression, sadness, and acute stress:
   (a) Depression/sadness: These emotional states can lead to irregular heartbeats, influenced by imbalances in neurotransmitters such as serotonin and norepinephrine.[9]
   (b) Acute stress: Sudden stress or shock can disrupt the normal heart rhythm, causing arrhythmias.[10]

4.2. Hormonal responses to emotions

Emotions directly impact the heart rate and rhythm through various hormonal responses.[11-13]

(i) Fear:
   (a) Heart rate: Increases.
   (b) Hormones: Adrenaline and cortisol.
   (c) Effects: Prepares the body for immediate action, increasing blood flow to muscles and heightening alertness.

(ii) Happiness:
   (a) Heart rate: Increases.
   (b) Hormones: Endorphins and dopamine.
   (c) Effects: Promotes the feelings of pleasure and well-being, thereby enhancing overall heart health.

(iii) Sadness:
   (a) Heart rate: May vary, potentially increasing or becoming irregular.
   (b) Hormones: Serotonin (imbalance) and cortisol.
   (c) Effects: Can result in decreased energy levels and mood disorders, which may impact heart rhythm.

(iv) Stress/anxiety:
   (a) Heart rate: Increases.
   (b) Hormones: Adrenaline and cortisol.
   (c) Effects: Sustained stress can lead to chronic high blood pressure and cardiovascular issues.

(v) Depression:
   (a) Heart rate: May become irregular.
   (b) Hormones: Serotonin and norepinephrine (imbalance).
   (c) Effects: Can result in chronic fatigue, sleep disturbances, and cardiovascular problems.

4.3. Heart health and mental states

The heart's response to our mental and emotional states highlights the profound connection between the mind and

the body. Our thoughts and emotions significantly influence the heart rate and rhythm, leading to various hormonal responses and physiological changes. This intricate relationship highlights the importance of managing stress, fostering positive emotions, and maintaining mental well-being for overall heart health.[14]

4.3.1. Stress and cardiovascular health

Chronic stress is a major risk factor for cardiovascular diseases. It triggers the release of stress hormones such as cortisol and adrenaline, which can elevate heart rate, blood pressure, and inflammation, contributing to long-term damage to the heart and blood vessels. Managing stress through relaxation techniques, exercise, and healthy lifestyle choices is crucial for maintaining heart health.[15]

4.3.2. Mindfulness practices

Mindfulness practices, which focus on bringing awareness to the present moment, have been shown to improve heart health by reducing stress, lowering blood pressure, and improving overall cardiovascular function. Techniques such as meditation, deep breathing, and yoga promote relaxation and emotional balance, positively impacting heart health.[16]

4.4. Case studies

(i) Meditation and heart health: Research has shown that individuals who practice meditation regularly have lower blood pressure and improved HRV, indicating enhanced ANS function and resilience to stress.
(ii) Yoga and cardiovascular function: Studies have demonstrated that yoga practitioners experience reduced heart rate and blood pressure, as well as improved overall cardiovascular health, attributed to the calming effects of yoga on the mind and body.

5. The metaphysical nature of consciousness

5.1. Qur'anic insights on the mind–heart connection

5.1.1. Qalb (قَلْب)—The heart as intellect and deliberation

In the Qur'an, the term *Qalb* is often used to describe the heart's role in intellect and deliberation. This usage emphasizes that the heart is not merely a physical organ, but also a center of understanding and reasoning. For example, in Surah Al-A'raf (7:179), it is stated: "They have hearts with which they do not understand, and they have eyes with which they do not see, and they have ears with which they do not hear. Those are like livestock; rather, they are more astray. It is they who are the heedless." This verse highlights the heart's cognitive function and its importance in guiding human behavior and consciousness.[1]

5.1.2. Fawad (فُؤَاد)—The heart as the seat of emotions

The Qur'an also uses the term *Fawad* to represent the heart as the seat of emotions. This concept is reflected in verses such as Surah Al-Isra (17:36), "And do not pursue that of which you have no knowledge. Indeed, the hearing, the sight, and the heart – about all those (one) will be questioned." Here, the heart is portrayed as central to emotional and sensory perception, emphasizing its role in processing and responding to emotional stimuli.[2]

5.1.3. Sadar (صَدْر)—The heart as the center of understanding and receptivity

In Qur'anic terminology, *Sadar* refers to the chest or breast and is often used to metaphorically describe the heart's receptivity and capacity for understanding. In Surah Az-Zumar (39:22), it states: "So is one whose breast Allah has expanded to (accept) Islam and he is upon a light from his Lord (like one whose heart rejects it)? Then, woe to those whose hearts are hardened against the remembrance of Allah. Those are in manifest error." This verse highlights the heart's role in spiritual and intellectual openness, aligning with the idea that thoughts and insights pass through the heart before manifesting in conscious actions.[3]

5.1.4. Qur'anic guidance for a calm heart

The Qur'an provides guidance on how the heart can achieve tranquility and calmness. In chapter 13, verse 28, it is mentioned, "Those who have believed and whose hearts are assured by the remembrance of Allah. Unquestionably, by the remembrance of Allah, hearts are assured." This verse highlights that the remembrance of Allah brings peace and calm to the heart, emphasizing the spiritual connection and the role of divine remembrance in achieving inner tranquility.[4]

5.2. The concept of *Nafs* and *Rooh*

5.2.1. Divine essence

The concept of *Rooh*, often translated as "soul" or "divine essence," is fundamental to understanding the metaphysical nature of consciousness. According to Islamic teachings, when God breathes the *Rooh* into the human body, it transforms into *Nafs*, which can be translated as "mind" or "self." This divine essence is immaterial and operates beyond the physical constraints of the body, indicating that consciousness is not confined to any physical locality.[5]

5.2.2. Immaterial nature of consciousness

Consciousness, as described in the Qur'an, transcends physical boundaries and exists as a state of mind, influenced by the divine essence. For instance, in chapter 5, verse 116, God uses the term *Nafsik*, derived from *Nafs*, to signify divine understanding and presence. This highlights the metaphysical connection between God and human consciousness, suggesting that true understanding and awareness originate from a divine source.[6] The Qur'anic distinction between *Khalq* (creation) and *Amr* (order) further supports this idea, as it separates the physical body from the immaterial divine essence.[7]

These Qur'anic insights align with ancient philosophical views and modern metaphysical research, emphasizing the profound interplay between the immaterial mind and the material body. By recognizing consciousness as a state of mind influenced by divine essence, we acknowledge the limitations of physical understanding and open ourselves to deeper, more complex realities governed by metaphysical principles.[8]

6. Cardiac memory and the heart's role in consciousness

6.1. Cardiac memory phenomenon

6.1.1. Understanding cardiac memory

The phenomenon of cardiac memory refers to the heart's ability to "remember" patterns of behavior and physiological responses even after medical interventions such as ablation therapy or transplant. This concept suggests that the heart is more than just a pump – it possesses intrinsic capabilities to retain information related to its previous states. Studies have demonstrated that patients who have undergone certain cardiac procedures still exhibit patterns of heart rhythms consistent with their pre-intervention states, indicating a form of memory embedded within the heart muscle itself.[1]

6.1.2. Implications for consciousness

The existence of cardiac memory supports the hypothesis that the heart plays a significant role in processing emotions and thoughts. If the heart can retain and recall specific patterns, it may also influence the overall state of consciousness by providing a foundation for emotional and cognitive experiences. This aligns with the idea that thoughts and emotions pass through the heart before affecting other parts of the body and that the heart serves as an important intermediary in the conscious experience.[2]

6.2. Case studies

6.2.1. David Bennett's pig heart transplant

A notable example supporting the concept of cardiac memory and the heart's role in consciousness involves David Bennett, a 57-year-old man who received a genetically modified pig heart transplant in January 2022. Despite the heart being of animal origin, Bennett's mind continued to function and direct his bodily actions, demonstrating that the heart can adapt to its new host while maintaining physiological functions.[3] This case highlights the argument that the heart, while crucial for physical circulation, is not the seat of consciousness. Instead, it acts as a tool utilized by the mind, which operates as an immaterial entity.[4]

6.2.2. Other anomalous cases

There are several extraordinary cases where individuals with significant brain damage or minimal brain structures continue to exhibit normal cognitive functions, further supporting the presence of an immaterial aspect of human consciousness. Examples include:

(i) Pam Reynolds' near-death experience: During complex brain surgery, Reynolds had a vivid near-death experience despite having no measurable brain activity, suggesting that consciousness extends beyond the brain.[5]
(ii) A man from France living with 10% of his brain: Despite a massive reduction in brain tissue, this individual maintained normal cognitive functions and led a regular life, challenging the conventional understanding of the brain's role in consciousness.[6]
(iii) Anencephaly and hydrocephalus cases: Individuals born without significant portions of their brain or with severe brain abnormalities often display unexpected cognitive abilities and awareness, indicating that consciousness may not be solely localized in the brain.[7]

These case studies illustrate the adaptability of the heart and its interaction with the mind, reinforcing the hypothesis that consciousness arises from a complex interplay between the heart, brain, and an immaterial mind.[8] They highlight the potential for the heart to influence conscious experience through its retained patterns and memory, further bridging the gap between the physical and metaphysical realms.[9]

7. Mind-heart coherence and its impact on health

7.1. HRV and cognitive flexibility

7.1.1. Research findings

HRV is a significant measure of the heart's ability to adapt to stress and maintain homeostasis. Higher HRV is associated with better overall health, emotional resilience, and cognitive flexibility, with studies showing that individuals with higher HRV are more adaptable to stress and exhibit improved emotional regulation and cognitive functions.[1,2]

HRV reflects the synchrony between the heart and the brain, indicating a coherent state where both organs are in optimal communication.[3]

7.1.2. Practical applications

Improving HRV through lifestyle changes and stress management techniques can lead to improved mental and physical health. Practices such as deep breathing exercises, physical activity, and biofeedback are effective in increasing HRV.[4,5] By fostering a state of coherence between the heart and mind, individuals can enhance their emotional stability and cognitive performance. This coherence is crucial for overall well-being, as it supports the body's ability to adapt to challenges and maintain internal balance.[6]

7.2. Mindfulness and heart health

7.2.1. Impact of mindfulness

Mindfulness practices have been shown to significantly improve heart health by reducing stress and promoting relaxation. Techniques such as meditation, yoga, and mindful breathing help regulate the ANS, reducing the dominance of the stress-response (sympathetic) system while enhancing the relaxation-response (parasympathetic) system.[7,8] These practices lead to lower blood pressure, reduced heart rate, and improved cardiovascular function.[9]

7.2.2. Case studies

(i) Meditation: Regular meditation practice has been associated with reduced blood pressure and increased HRV, indicating improved autonomic regulation and reduced stress levels.[10]
(ii) Yoga: Yoga practitioners often show lower resting heart rates and improved cardiovascular resilience, attributed to the combined physical, mental, and emotional benefits of the practice.[11]
(iii) Mindfulness-based stress reduction (MBSR): Programs such as MBSR have been widely implemented to help individuals manage stress and improve heart health.[12] MBSR combines mindfulness meditation and yoga to cultivate awareness and reduce stress. Participants in MBSR programs often report significant improvements in their emotional well-being and physical health, including enhanced heart function and reduced risk of cardiovascular disease.[13]

7.3. Spiritual heart and intuition

7.3.1. Wisdom traditions

Various spiritual traditions recognize the heart as the center of wisdom and intuition. These traditions suggest that the heart is not only a physical organ but also a source of deep insight and guidance.[14] Practices such as heart-centered meditation and heart coherence techniques aim to align the heart and mind, facilitating access to deeper states of consciousness and intuitive knowledge.[15]

7.3.2. Heart-centered meditation

Heart-centered meditation focuses on bringing awareness to the heart, fostering a sense of peace, compassion, and connection. This practice involves visualizing the heart as a source of light and love, allowing individuals to tap into their inner wisdom and intuition. Research has shown that heart-centered meditation can enhance emotional well-being, reduce stress, and improve overall health.[16]

7.3.3. Heart coherence techniques

Heart coherence techniques involve synchronizing the heart's rhythmic patterns with positive emotional states. By focusing on feelings of gratitude, love, and compassion, individuals can achieve a state of coherence in which the heart and mind are harmoniously aligned. This state of coherence has been associated with improved emotional regulation, cognitive function, and physical health.[16]

8. The dual control of the physical and metaphysical realms

8.1. Intention and action

8.1.1. Role of intention

Intention is a unique and crucial attribute of the mind, which uses the physical body as a tool to perform actions. In Islamic divine philosophy, it is revealed that the mind, as an extension of the divine essence (*Rooh*), influences the physical world through intentions.[1] The mind is accountable for these deeds in the afterlife, as stated in divine texts.[2] This concept is supported by Qur'anic teachings, which emphasize that the mind (*Nafs*) perceives and influences the physical world through intention. For instance, in Surah Al-Imran (3:154), it is mentioned, "[It was] so that Allah might test what is in your breasts and purify what is in your hearts." This verse highlights the role of intention and the heart's responsiveness to mental states.[3]

8.1.2. Mind-body connection in metaphysical terms

The mind–body connection is not confined to physical interactions but extends into the metaphysical realm. The heart and brain are tools through which the immaterial mind expresses itself.[4] Thoughts and intentions first affect the heart, which then influences other parts of the body. This sequence is supported by the idea that the heart's electromagnetic field and hormonal responses are directly influenced by mental states.[5] The metaphysical influence of the mind highlights the dual control mechanism over the

physical world, where metaphysical forces shape physical actions and experiences.[6]

8.2. The interplay of physical and metaphysical realms

8.2.1. Qur'anic perspectives

The Qur'an provides profound insights into the interplay between the physical and metaphysical realms. It distinguishes between *Khalq* (creation) for the physical body and *Amr* (order) for the divine essence, highlighting the dual nature of human existence.[7] The *Rooh* (divine essence), when breathed into the human body, becomes *Nafs* (mind), an immutable connection between the divine and the material.[8] This connection illustrates that while the physical world operates under natural laws, it is simultaneously influenced and controlled by metaphysical forces. For example, in Surah Al-Hajj (22:46), it is stated, "So have they not traveled throughout the earth and have hearts by which to reason and ears by which to hear? For indeed, it is not the eyes that are blinded but blinded are the hearts which are within the breasts." This verse emphasizes the heart's role in understanding and reasoning, influenced by the metaphysical mind.[9]

8.2.2. Scientific and philosophical integration

Integrating scientific research with philosophical inquiry provides a comprehensive understanding of the dual control of the physical and metaphysical realms. The heart's electromagnetic field, neurocardiology, and cardiac memory phenomena support the idea that the heart plays a significant role in shaping physical and mental states.[10] Philosophical perspectives, such as those from ancient Greek, Egyptian, Chinese, and Indian traditions, align with the idea that the heart is central to human experience, processing thoughts and emotions before influencing the brain and body.[11]

8.2.3. Metaphysical influence on physical actions

The metaphysical realm, governed by the divine essence, exerts control over physical actions through the mind's intentions. This dual control mechanism is evident in the way mental states influence heart rhythms, hormonal responses, and overall health.[12] The concept of the heart as a tool of the mind aligns with the idea that thoughts and intentions are first processed by the heart, which then affects physical actions and experiences.[13] This understanding bridges the gap between physical laws and metaphysical principles, providing a holistic view of human consciousness and behavior.[14]

By recognizing the dual control of the physical and metaphysical realms, we gain deeper insights into the nature of existence and the intrinsic role of metaphysical forces in shaping the physical world. This perspective invites further exploration into the profound connection between the mind, heart, and body, highlighting the need to integrate scientific, philosophical, and spiritual knowledge to fully understand human nature.[15]

9. Conclusion

This paper integrates scientific research, philosophical perspectives, and Qur'anic insights to present a comprehensive understanding of the mind-heart connection. By challenging the conventional brain-centric view of consciousness and emphasizing the heart and brain as the tools of the soul (divine essence) or mind, this study offers a holistic perspective on human nature.[1]

The findings highlight the profound interplay between the physical and metaphysical realms, suggesting that thoughts and emotions originate in the mind, pass through the heart, and subsequently influence other parts of the body. This sequence highlights the heart's crucial role in processing and mediating conscious experiences.[2]

Recognizing the dual control of the physical and metaphysical realms invites further exploration into the nature of consciousness and the limits of physical understanding. Future research should focus on integrating diverse perspectives and methodologies to enhance understanding of this intricate connection.[3] By bridging the gap between science, philosophy, and spirituality, deeper insights into human existence and the intricate relationship between the mind, heart, and body can be obtained.[4]

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Further disclosure

This research presents a novel concept that challenges traditional views in neuroscience. It is anticipated to bring significant advancements and new perspectives to the field.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Causal association between constipation and white matter microstructure: A Mendelian randomization study

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Abstract

Constipation, a prevalent gastrointestinal issue, has been linked to neurological health through the gut–brain axis (GBA). This study investigated the genetic association between constipation and white matter (WM) microstructure using a two-sample bidirectional Mendelian randomization (MR) approach. Genetic instruments for constipation were derived from the FinnGen study (41,124 cases and 371,057 controls). Summary statistics for diffusion tensor imaging parameters, including fractional anisotropy (FA) and mean diffusivity (MD), were obtained from the UK Biobank (33,292 subjects). The primary MR analysis used the inverse variance weighted (IVW) method, with supplementary analyses including weighted median, constrained maximum likelihood, and robust adjusted profile score methods. Sensitivity analyses, including Cochran's *Q* test and MR-Egger regression, assessed heterogeneity and pleiotropy. Two WM imaging-derived phenotypes showed significant causal associations with constipation. Specifically, a higher second MD principal component of the superior longitudinal fasciculus (SLF) showed a significant protective effect against constipation (odds ratio [OR]=0.71, 95% confidence interval [CI]=0.58 – 0.87, $p=7.55\times10^{-4}$). Conversely, higher FA in the anterior corona radiata (ACR) increased constipation risk (OR=1.33, 95% CI=1.11 – 1.60, $p=2.13\times10^{-3}$). No significant causal effect of constipation on WM microstructure was found. All supplementary analyses corroborated the IVW results, indicating robustness and consistency. Sensitivity analyses showed low heterogeneity and no significant directional pleiotropy. This study provides strong evidence for a genetic association between specific WM microstructures and constipation, emphasizing the role of the SLF and ACR in the GBA. These findings highlight the need to consider neurological factors in understanding and managing constipation and warrant further research into the underlying mechanisms and broader implications of the GBA.

Keywords: Constipation; White matter; Diffusion tensor imaging; Mendelian randomization; Gut-brain axis

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1. Introduction

Constipation, characterized by infrequent or difficult bowel movements, is one of the most common gastrointestinal complaints worldwide.[1] While constipation is often perceived as a benign condition, emerging evidence suggests its potential impact on neurological health. Psychological factors, including stress and anxiety, may also influence bowel habits, suggesting a bidirectional relationship between the brain and the gastrointestinal system.[2] However, the underlying mechanisms linking constipation to these neurological outcomes remain poorly understood. The intricate interplay between gastrointestinal health and neurological function has garnered increasing attention in recent years, particularly to the gut–brain axis (GBA) – a bidirectional communication system.[3] This axis governs essential physiological functions and homeostasis, extending beyond conventional organ-specific domains to influence a myriad of bodily processes.[1,4] Disruption of GBA equilibrium has been implicated in various disorders, including gastrointestinal, psychiatric, and neurological conditions.[1] Understanding the mechanisms underlying this axis is crucial for elucidating the pathophysiology of these disorders and developing targeted interventions.

Diffusion tensor imaging (DTI), a non-invasive neuroimaging technique, enables the characterization of white matter (WM) microstructure in the brain. DTI measures the diffusion of water molecules in brain tissue, providing insights into the organization and integrity of WM tracts.[5] WM microstructure, composed of axonal fibers and myelin sheaths, plays a crucial role in facilitating communication between brain regions.[6] Alterations in WM microstructure detected by DTI have been associated with a wide range of neurological conditions, including neurodegenerative diseases, psychiatric disorders, and neurodevelopmental disorders,[7,8] highlighting its importance as a biomarker of brain health. Besides, DTI has been instrumental in elucidating the neurobiological underpinnings of functional gastrointestinal disorders (FGIDs), such as functional constipation and irritable bowel syndrome (IBS). Studies have demonstrated WM alterations in regions associated with pain processing and emotional regulation among individuals with FGIDs, highlighting the bidirectional influence of gastrointestinal health on brain structure and function.[9,10] However, the causal relationship between changes in brain structure and the occurrence of these diseases is still unclear.

Recent advances in genetics and neuroimaging have provided valuable tools for investigating the complex interactions within the GBA. Mendelian randomization (MR) is a statistical method that utilizes genetic variants as instrumental variables (IVs) to assess causality in observational data. By leveraging genetic variants that are randomly allocated at conception and remain fixed throughout life, MR mimics the randomization process in a randomized controlled trial.[11] MR studies have gained prominence in elucidating causal relationships in complex traits and diseases, where traditional observational studies are often limited by confounding and reverse causation.[12,13] MR studies have revealed causal relationships between the digestive system and nervous system, for example, between inflammatory bowel disease and Alzheimer's disease,[14] between IBS and leisure sedentary behavior,[15] and between gut microbiota and multiple sclerosis.[16] However, the application of MR in elucidating causal relationships between constipation and WM microstructure remains limited.

Motivated by the bidirectional nature of the GBA and the potential implications of constipation for neurological outcomes – and recognizing the role of the GBA in the shared genetic etiology of FGIDs and psychiatric conditions[17] — we conducted a two-sample bidirectional MR study to investigate the genetic association between constipation and WM microstructure at a microscopic level. This study aimed to deepen our understanding of the complex interactions between gastrointestinal health and neurological characteristics, with implications for both research and clinical practice.

2. Methods

2.1. MR and the associated assumptions

MR is a method used to assess causal relationships between risk factors and health outcomes using genetic variants as IVs. This approach relies on three core assumptions: (1) Relevance: The genetic variants used as IVs must be associated with the exposure (constipation); (2) Independence: The genetic variants must not be associated with confounders of the exposure-outcome relationship; and (3) Exclusion restriction: the genetic variants must affect the outcome (WM microstructure) only through the exposure and not through alternative pathways. These assumptions help mitigate confounding and reverse causation, making MR a powerful tool for causal inference in epidemiology.

2.2. Data sources and study population

In our study, we obtained summary-level data for constipation from the FinnGen project, which includes 41,124 cases and 371,057 controls. The FinnGen study combines nationwide biobank data with structured national health-care records, leveraging a unique, relatively homogeneous population for robust genetic analysis.[18]

For WM microstructure, genome-wide association study (GWAS) summary statistics of DTI parameters were

sourced from the UK Biobank. This dataset encompasses 33,292 subjects and includes measures of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity, radial diffusivity, mode of anisotropy, mean (averaged parameters), providing a comprehensive characterization of brain WM.[19] Principal component (PC) analysis was applied to the DTI parameters of each WM tract to reduce data dimensionality and extract PCs that capture the most significant sources of variation. The PCs were derived from multiple DTI metrics measured along each tract and ordered according to the amount of variance they explained. These PCs accounted for a considerable proportion of the variance in the corresponding DTI parameters and were mapped onto established WM tracts based on the anatomical localization of the DTI measurements. Detailed information about the DTI parameters and WM tracts used in this study is presented in Supplementary Table S1.

2.3. Selection of IVs

We implemented stringent quality assurance measures, including careful selection and refinement of genetic instruments, comprehensive sensitivity analyses to validate results, and consistent data harmonization and monitoring throughout the analysis phase. IVs were selected based on their strong association with constipation in the GWAS dataset. Single nucleotide polymorphisms (SNPs) reaching genome-wide significance ($p<5\times10^{-8}$) were considered potential IVs. To ensure the relevance assumption of the MR, we applied linkage disequilibrium clumping with a threshold of $r^2<0.001$ and a window size of 10,000 kb to ensure independence among the selected SNPs.

2.4. Statistical analysis

The inverse variance weighted (IVW) method[20] was utilized as the primary analysis approach to estimate the causal effect of constipation on WM microstructure. This method combines the Wald ratios of individual SNPs to produce an overall estimate of the causal effect. To ensure the robustness of the IVW estimates, additional MR methods, including the weighted median method,[11] the constrained maximum likelihood (cML) method,[20] and the robust adjusted profile score (RAPS) method,[21] were employed. A Bonferroni-corrected p-value threshold of 2.38×10^{-3} (0.05/21, where 21 represents the number of WM tracts analyzed) was applied to account for multiple comparisons. Cochran's Q test and the I^2 statistic were used to assess heterogeneity among SNP-specific estimates. Evidence of heterogeneity indicates potential violations of MR assumptions due to variability in SNP-specific causal effect estimates.

To detect and account for directional pleiotropy – where genetic variants affect the outcome through pathways other than the exposure – we conducted MR-Egger regression. A significant intercept ($p<0.05$) would indicate the presence of directional pleiotropy. All statistical analyses were performed using R software (version – 4.3.0, The R Development Core Team, New Zealand), with the "MendelianRandomization" and "TwoSampleMR" packages.

3. Results

The overall design of the present study is shown in Figure 1. Our results revealed that two WM imaging-derived phenotypes (IDPs) demonstrated significant causal effects on constipation (Figure 2A). Specifically, the MD PC of the superior longitudinal fasciculus (SLF) showed a significant protective effect against constipation. This was evidenced by a 29% reduction in the genetic susceptibility to constipation (IVW method: odds ratio [OR]=0.71, 95% confidence interval [CI]=0.58 – 0.87, $p=7.55\times10^{-4}$). This finding indicates that higher MD in this WM tract is associated with a decreased risk of developing constipation. Conversely, the fifth FA PC in the anterior corona radiata (ACR) was found to be associated with an increased risk of constipation. Specifically, higher FA in this region was associated with a 33% increase in the odds of constipation (OR=1.33, 95% CI=1.11 – 1.60, $p=2.13\times10^{-3}$) (Figure 2B). This suggests that microstructural alterations in the ACR, as reflected by FA, may contribute to a higher susceptibility to constipation. In contrast, our analysis did not reveal any significant causal effect of constipation on alterations in WM microstructure. This suggests that while specific WM microstructure characteristics can influence the risk of constipation, the reverse – constipation influencing WM microstructure – was not supported by our data.

To ensure the robustness of our primary findings, we performed additional MR analyses using the weighted median, cML, and RAPS methods. These supplementary analyses corroborated the IVW results, indicating the consistency and reliability of the observed associations. Further sensitivity analyses assessed the presence of heterogeneity and pleiotropy. Cochran's Q test and I^2 statistic indicated low heterogeneity among the SNPs used in the IVW estimates, suggesting consistent causal estimates across SNPs. In addition, MR-Egger regression did not show significant evidence of directional pleiotropy, as the intercepts were not significantly different from zero ($p>0.05$).

The leave-one-out analyses confirmed that no individual SNP significantly dominated the causality estimates. Further scrutiny using scatter plots, funnel plots, and forest plots revealed no considerable heterogeneity (Supplementary Figures S1 and S2).

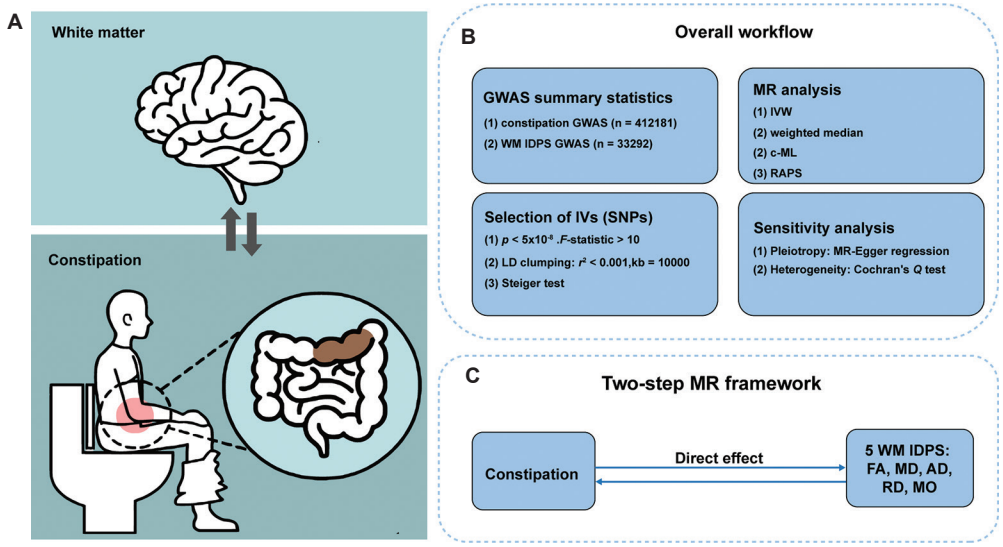


Figure 1. Overview of the study design and analysis. (A) Schematic illustration of the bidirectional relationship between constipation and WM microstructure. (B) Analytical workflow of the MR analysis. (C) The two-sample MR analysis framework, evaluating the direct causal effect of constipation on five WM IDPs.

Abbreviations: ACR: Anterior corona radiata; AD: Axial diffusivity; cML: Constrained maximum likelihood; DTI: Diffusion tensor imaging; FA: Fractional anisotropy; GWAS: Genome-wide association study; IDP: Imaging-derived phenotype; IV: Instrumental variable; IVW: Inverse variance weighted; LD: Linkage disequilibrium; MD: Mean diffusivity; MO: Mode of anisotropy; MR: Mendelian randomization; RAPS: Robust adjusted profile score; RD: Radial diffusivity; SLF: Superior longitudinal fasciculus; SNP: Single-nucleotide polymorphism; WM: White matter.

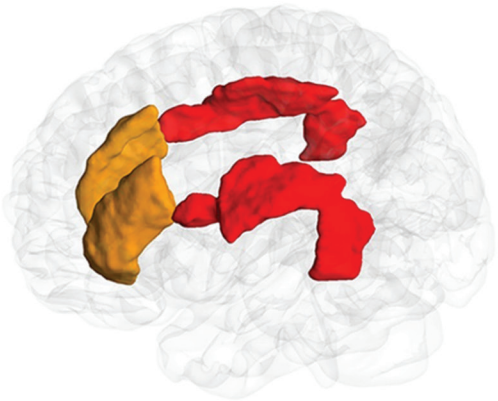
4. Discussion

Our study provides significant insights into the genetic associations between constipation and specific WM microstructures. The identified WM tracts, such as the SLF and ACR, are frequently implicated in advanced brain functions such as cognition, emotion, and behavior.[22] The utilization of DTI measures such as MD and FA to evaluate WM integrity highlights the intricate interplay between brain structure and gastrointestinal health.[23]

The SLF is a prominent WM tract connecting the frontal, parietal, and occipital lobes, playing a critical role in various cognitive processes, including language, attention, and working memory.[24] Our findings reveal that higher MD in the SLF is associated with a reduced genetic susceptibility to constipation. MD reflects the rate of water diffusion within tissue and provides an index of microstructural integrity.[25] An increased MD in the SLF may indicate a healthier WM microstructure, potentially enhancing coordination of GBA signaling pathways, and thereby reducing the risk of constipation. Conversely, the ACR, a tract involved in emotional regulation and executive functions, showed an increased risk of constipation in individuals with higher FA values. FA measures the directional coherence of water diffusion, indicating the integrity and density of WM fibers.[26] The observed association between higher FA in the ACR and increased constipation risk suggests that microstructural alterations in this region could disrupt normal gut–brain communication, leading to gastrointestinal dysfunction. This finding aligns with previous research highlighting the role of the ACR in emotional and autonomic regulation, both of which are crucial for maintaining gut motility.[27] The SLF and ACR may influence autonomic and enteric nervous system functions through their connections with brain regions involved in emotional and cognitive processing. These pathways are essential for regulating gut–brain communication and gastrointestinal regulation. Potential mechanisms underlying the observed associations include modulation of autonomic pathways, stress-related or emotional regulation via fronto-limbic circuits, neuroinflammation, and variations in vagal tone. For instance, the SLF's role in cognitive processes could affect autonomic regulation of the gut, while the ACR's involvement in emotional regulation might impact gut motility through fronto-limbic circuits. Neuroinflammatory processes and variations in vagal tone may further mediate the bidirectional communication of GBA, potentially explaining the genetic associations we identified.

The GBA is a complex bidirectional communication network that links the enteric and central nervous systems through hormonal, immunological, and neural pathways.[4] Our results highlight the importance of this axis in the pathophysiology of constipation. The involvement of specific WM tracts in influencing constipation risk

A



B

IDP (ID)	No. SNPs	OR (95% CI)	*p* value	MR-Egger intercept *p* value
The second MD PC of SLF				
IVW	3	0.71 (0.58-0.87)	7.55×10^{-4}	
Weighted median	3	0.73 (0.58-0.93)	9.98×10^{-3}	0.701
c-ML	3	0.70 (0.55-0.87)	1.81×10^{-3}	
RAPS	3	0.71 (0.57-0.89)	2.68×10^{-3}	
The fifth FA PC of ACR				
IVW	3	1.33 (1.11-1.60)	2.13×10^{-3}	
Weighted median	3	1.28 (1.01-1.61)	4.24×10^{-2}	0.409
c-ML	3	1.32(1.09-1.60)	4.32×10^{-3}	
RAPS	3	1.34 (1.09-1.63)	4.89×10^{-3}	

Figure 2. (A) Anatomical locations of the regional WM microstructure show significant causal associations with constipation in the primary MR analysis. SLF is shown in red and ACR is shown in orange. (B) Forest plots exhibiting the causal estimates with ORs and their corresponding 95% CIs are shown on the x-axis. Significant causal correlations ($p<2.38\times10^{-3}$ after Bonferroni correction) are highlighted in red. MR analyses were conducted -using IVW, weighted median, cML, and RAPS methods.

Abbreviations: ACR: Anterior corona radiata; CI: confidence interval; c-ML: Constrained maximum likelihood; FA: Fractional anisotropy; IDP: Imaging-derived phenotype; IVW: Inverse variance weighted; MD: Mean diffusivity; MR: Mendelian randomization; OR: Odds ratio; PC: Principal component; RAPS: Robust adjusted profile score; SLF: Superior longitudinal fasciculus; SNP: Single nucleotide polymorphism; WM: White matter.

underscores the need for integrated models that consider both the neurological and gastrointestinal dimensions of this condition. Given the bidirectional nature of the GBA, gastrointestinal disturbances such as constipation can lead to alterations in brain structure and function, while neurological changes can impact gut motility and function.[3,28] This interplay suggests that interventions targeting one component of the GBA may have profound effects on the other, highlighting the potential for holistic treatment approaches.[1]

The findings of our MR study carry several important clinical and research implications. First, they suggest that targeting WM microstructure may serve as a novel therapeutic approach for managing constipation. For example, interventions aimed at enhancing the integrity of the SLF could potentially reduce constipation risk. In addition, understanding the genetic basis of these associations could inform personalized medicine strategies, where individuals at high genetic risk of constipation could receive targeted interventions to prevent or manage the condition.[29,30] Further research is necessary to validate our findings and explore the underlying mechanisms linking WM microstructure and constipation. Longitudinal studies tracking changes in WM integrity alongside constipation onset and progression would be particularly valuable. Moreover, exploring the role of other WM tracts and their interactions within the broader GBA could provide deeper insights into the systemic nature of these associations.[3,17] The application of advanced neuroimaging techniques, such as DTI, in larger and more diverse populations will enhance the generalizability of our findings.[31,32] In addition, integrating neuroimaging data with other omics approaches, such as genomics, proteomics, and metabolomics, could offer a more comprehensive

understanding of the biological pathways involved.[33,34] Future studies may also benefit from implementing region-specific imaging analyses to more precisely delineate the relationship between WM alterations and constipation. Our findings pave the way for exploring behavioral or neuromodulatory interventions targeting WM structures such as the SLF and ACR. Potential approaches may include stress management techniques, cognitive-behavioral therapies, or non-invasive electrical neuromodulation methods aimed at improving gut–brain communication and reducing constipation risk.

Despite providing novel insights, our study has several limitations. The use of summary-level data in MR analyses limits our ability to explore more nuanced relationships between specific genetic variants and WM microstructure. Future investigations using individual-level data could provide a more detailed understanding of the genetic architecture underlying these associations. Moreover, although MR is a powerful tool for causal inference, it depends on several core assumptions. Violations of these assumptions, particularly the presence of horizontal pleiotropy – where genetic variants influence the outcome through pathways independent of the exposure – could bias our results. Although we employed methods such as MR-Egger regression to detect and account for pleiotropy, these methods have their own limitations. Future studies should also consider the potential impact of environmental and lifestyle factors on the GVA. Factors such as diet, physical activity, stress, and medication use are known to influence both gastrointestinal and neurological health. These factors may interact with genetic predispositions to modulate the risk of constipation. Understanding these interactions could help in developing more effective and personalized treatment strategies. Last but not least, our samples were restricted to individuals from the European population, which may limit the generalizability of our findings to other populations. Replication studies in more diverse cohorts are needed to confirm the relevance of these associations across different ethnic groups.

5. Conclusion

This MR study provides robust evidence for a genetic association between specific WM microstructures and constipation. The involvement of WM tracts, such as the SLF and ACR, highlights the complex interplay between brain and gut health. These findings underscore the importance of considering both neurological and gastrointestinal factors in understanding and managing constipation. Future research should focus on validating these findings, exploring the underlying mechanisms, and considering the broader context of the GBA to develop comprehensive and effective therapeutic approaches.

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Conflict of interest

The authors declare no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data are publicly available. The data sources for this study include the FinnGen consortium (https://r10.finngen.fi/) and BIG-S2 (https://www.med.unc.edu/bigs2/data/gwas-summary-statistics/).

Further disclosure

Part of the findings have been presented at the 30th Annual Conference of the Psychosomatic Medicine Branch of the Chinese Medical Association in Fuzhou, China.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Cross-cultural insights into psychosomatic symptoms, depression, and anxiety: A comparative study of China and Pakistan

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Abstract

Psychosomatic refers to an illness in which stress causes or exacerbates physical symptoms, and it may occur in transient or along with more acute mood disorders. The current study aimed to enhance understanding of the prevalence and cultural factors affecting psychosomatic symptoms, depression, and anxiety in China and Pakistan. A comparative cross-cultural study was conducted using a non-probability sampling technique. A total of 1633 samples were collected, including 598 healthy controls (300 from China and 298 from Pakistan) and 1035 patients (521 from China and 514 from Pakistan). Three assessment tools were utilized: Psychosomatic symptom scale (PSSS), patient health questionnaire-9, and generalized anxiety disorder-7. There were significant differences in the symptoms of patients and control groups with psychosomatic symptoms, depression, and anxiety in both countries. *Post hoc* testing revealed that Pakistani patients with mood disorders reported more psychosomatic symptoms than Chinese patients ($p<0.001$), whereas the Chinese control group had more psychosomatic symptoms than the Pakistani control group ($p=0.001$). Analysis of PSSS ratings in Chinese patients demonstrated a strong correlation between "depressed mood" and "loss of interest." Pakistani PSSS displayed strong correlations on the somatic subscale and psychological subscale. In the present study, Pakistani patients exhibited higher levels of psychosomatic complaints, depression, and anxiety compared to Chinese patients. Notably, network analysis reveals that Pakistani patients displayed more physical symptoms, whereas Chinese patients experienced more psychological symptoms.

Keywords: Psychosomatics; Depression; Anxiety; Cross-cultural; China; Pakistan; Network analysis

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1. Introduction

The relationship between psychological and physical symptoms is complex, and more studies in this area are necessary from a cultural perspective. The term "psychosomatic" refers to an illness in which stress causes or exacerbates physical symptoms, and it may occur in transient or along with more acute mood disorders.[1-3] Somatization refers to a condition where psychological or emotional distress manifests as physical symptoms that cannot be fully explained by a medical condition.[4] These disorders arise from the complex interaction of biological, psychological, and social factors, with stress and emotional conflict often playing key roles in symptom development and maintenance.[5] The biopsychosocial model, proposed by Engel,[6] highlights the importance of understanding this interplay, as emotional stress can affect bodily systems, such as the autonomic nervous system and immune response. Individuals with psychosomatic disorders may experience a wide range of symptoms – headaches, body pain, gastrointestinal issues, and fatigue – without an identifiable medical cause. Treatment can be challenging and often requires a multidisciplinary approach.[6,7]

It is thought that in psychosomatic disorders, patients may focus on their physical symptoms as a way to minimize psychological pain at times of stress.[8] The biopsychosocial model posits that an individual's health, psychological state, and social environment are interconnected, contributing to the development of somatic symptom disorders. Psychosomatic disorders arise from the interplay of biological, psychological, and social factors, often accompanied by emotional distress stemming from one's circumstances.[9] Mental health problems, including anxiety, depression, and other psychosomatic conditions, have been reported a significant global rise from 2000 to 2018,[9] resulting in increased health-care costs.[10] A study conducted in China in three waves (i.e., in February 2020, March 2020, and April 2022, respectively) reported that the prevalence of psychosomatic disorders was 22%, 28%, and 39%, respectively.[11] In this regard, the psychosomatic approach has gained the interest of physicians and clinicians, consequently forming various subdisciplines, including functional neurology, psycho-immunology, psycho-nephrology, psycho-oncology, psycho-dermatology, and psycho-neuroendocrinology, among others. These subdisciplines have established dedicated medical journals, scientific societies, and clinical services.[12,13]

Psycho-neuroimmunology and psycho-oncology have seen significant advancements in China and Pakistan, with a focus on the relationship between psychological factors and physical health. In China, the Psycho-neuroimmunology Research Society has expanded in the Asia–Pacific region, emphasizing research on stress and immune function.[14] In Pakistan, studies link psychological stress, especially from large-scale disasters, to suppressed immune responses.[15] Psycho-oncology in China integrates psychosocial measures into cancer care,[16] while Pakistan highlights the need for multidisciplinary tumor boards to address the psychosocial impacts of cancer.[17] Both countries have demonstrated significant progress in psycho-dermatology and psycho-neuroendocrinology. Chinese studies have reported untreated depression and anxiety in dermatological patients,[18] whereas Pakistan is raising awareness of mental health issues related to skin conditions.[19] Research on psycho-neuroendocrinology in both nations examines the impact of stress on the hypothalamic-pituitary-adrenal axis, emphasizing interventions such as exercise. Cultural factors, including family systems, marriage practices, language, religion, beliefs, and social events, significantly influence psychosomatic symptoms in the distinct contexts of China and Pakistan.[20]

Psychosomatic symptoms are common in both chronically ill and reasonably healthy individuals. Conditions, such as diabetes, hypertension, and cardiovascular diseases, often involve somatic symptoms linked to mood.[21] Patients with chronic illnesses frequently experience psychosomatic symptoms that can exacerbate their conditions, increase health-care costs, and reduce their quality of life.[22,23] For instance, individuals with fibromyalgia or irritable bowel syndrome often suffer from overlapping psychological and somatic symptoms, complicating their management and treatment.[24,25] Addressing these psychosomatic symptoms through integrated care approaches can significantly improve patient outcomes and reduce the burden on health-care systems.

Although there has been a growing interest in the social, economic, and political ties between China and Pakistan, especially through projects such as the China–Pakistan Economic Corridor, relatively little attention has been given to the psychological aspects of this relationship.[26,27] Thus far, most research has focused on cross-cultural business practices and diplomacy, but there is a noticeable lack of studies that investigate behavioral and mental health issues, particularly psychosomatic disorders, depression, and anxiety, in both countries. Psychosomatic disorders have been extensively researched in Western populations, including the field of functional neurology, but there is a notable lack of studies focusing on Asian populations. Hence, the present research aims to address this significant gap in the literature. Significant differences in the medical expression of disorders

primarily emerge across Asian countries; for instance, the unique sociocultural, economic, and religious landscapes of nations such as China and Pakistan profoundly influence how psychosomatic symptoms are experienced and understood. Examining these influences offers the potential to unlock groundbreaking perspectives. The study's findings could significantly enhance cultural competence among health-care professionals, empowering them to deliver truly patient-centered care that honors and integrates cultural differences in symptom expression and treatment preferences. Psychosomatic symptoms often lead to repeated medical visits, unnecessary diagnostic procedures, and excessive treatments, all of which escalate healthcare costs. By exploring these symptoms through a cultural lens, this research could help mitigate such challenges. Furthermore, it would make a vital contribution to the growing field of cross-cultural mental health, shedding light on underexplored populations, such as those in China and Pakistan. The insights gained may also resonate with other cultures sharing similar sociocultural dynamics, thereby advancing the global understanding of psychosomatic symptoms and their management.

This study investigated the prevalence of psychosomatic symptoms, depression, and anxiety among Chinese and Pakistani patients, aiming to reveal the profound impact of cultural factors on mental health. By examining these differences, the research aspires to shape culturally attuned clinical practices and mental health policies. The contrasting cultural norms, societal structures, economic conditions, and educational systems of China and Pakistan may significantly shape the manifestation of psychosomatic symptoms, depression, and anxiety. The findings hold the potential to drive the development of targeted mental health interventions and policies tailored to the unique needs of each country. Our investigation in this study was based on several hypotheses: (i) Chinese patients exhibit significantly lower levels of psychosomatic symptoms compared to Pakistani patients; (ii) Pakistani patients have significantly higher levels of depression than Chinese patients; and (iii) Chinese patients have significantly lower levels of anxiety compared to Pakistani patients.

2. Methods

2.1. Participants

The study was approved by the Ethics Committee of Zhongda Hospital, Southeast University (registration no. 2021ZDSYLL347-P01). During this cross-cultural study, data were gathered from both China and Pakistan using a non-probability sample technique. This approach was chosen due to its practicality in accessing patients and control participants within hospital settings, particularly where random sampling was not feasible. This study included 1633 participants, consisting of a control group of 598 individuals (300 from China and 298 from Pakistan) and a patient group of 1035 individuals (521 from China and 514 from Pakistan). In China, the participants were selected from 14 centers, and all subjects were asked to sign a written informed consent form. In Pakistan, the participants were selected from both outpatient and inpatient departments at two centers. The inclusion criteria for the patients were: (i) either the outpatient or inpatient department; (ii) age over 18 years; and (iii) diagnosed with one of the following disorders: generalized anxiety disorder (GAD), major depressive disorder, somatic symptom disorder, panic disorder, coronary heart disease, hypertension, peptic ulcer, hyperthyroidism, diabetes, cancer, asthma, or other psychosomatic disorders reviewed by trained researchers. The exclusion criteria for the patients were: (i) psychiatric disorders that caused suicidal behavior or aggression; and/or (ii) severe diseases, such as uremia, respiratory failure, acute cerebral infarction, and acute myocardial infarction. The inclusion criteria of healthy controls were: (i) age over 18 years; and (ii) willingness to sign the informed consent form. The exclusion criteria were: (i) no history of psychiatric disorder; and/or (ii) no current diagnosis of acute physical disease.

2.2. Assessment tools

To assess psychosomatic symptoms, depression, and anxiety in the current study, three scales were utilized. The psychosomatic symptom scale (PSSS) was used to measure psychosomatic symptoms, whereas the patient health questionnaire-9 (PHQ-9) and GAD-7 were used to measure signs of depression and anxiety, respectively. In China, these questionnaires have demonstrated strong validity and reliability in their Chinese-language version; in Pakistan, the Urdu versions of these questionnaires have relatively fair validity and reliability.

The PSSS is a short self-rated questionnaire measuring both psychological (P-subscale) and somatic symptoms (S-subscale) over the past 4 weeks, with several response categories: "never" scored as 0, "several days a week or rarely" scored as 1, "more than half the day" scored as 2, and "every day or whole day or most of the time" scored as 3. The PSSS scale comprises 26 items, with 19 items evaluating somatic symptoms (S-subscale) related to urogenital, neurological, digestive, pulmonary, and other organ systems. The remaining seven items in the P-subscale assess anxiety, depression, obsessive-compulsive symptoms, suicidal thoughts, and anger.[28,29] The Urdu version of the PSSS demonstrated high reliability, with a Cronbach's alpha of 0.974,[28] whereas the Chinese version has a Cronbach's alpha of 0.907.[29]

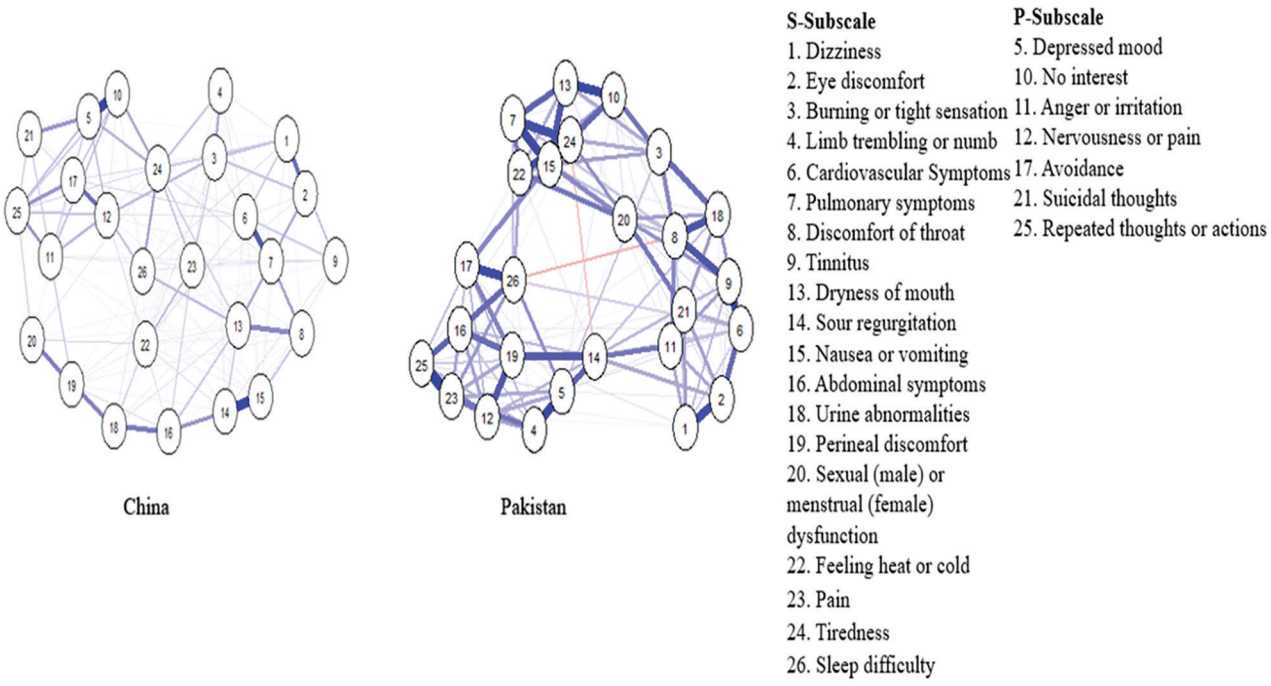

Figure 1. Network structure of the psychosomatic symptom scale (PSSS)
Abbreviations: P-subscale: Psychological subscale; S-subscale: Somatic subscale.

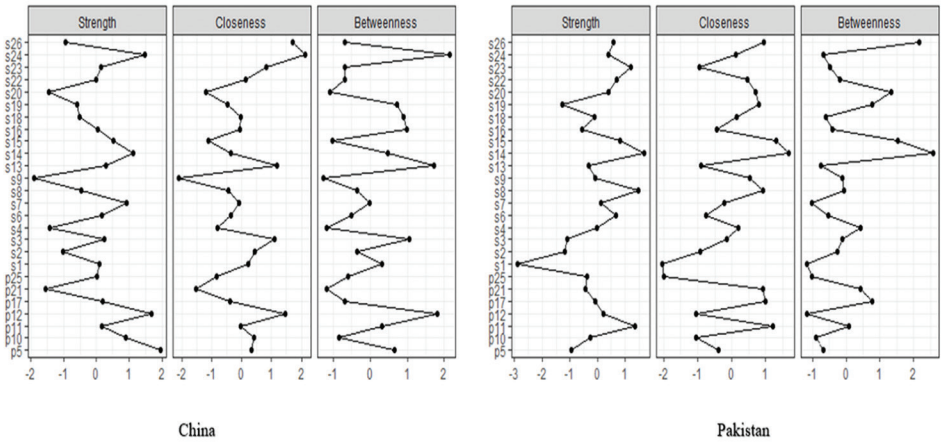

Figure 2. Centrality indices of the psychosomatic network structure in China and Pakistan

The PHQ-9 is a valid and reliable instrument for screening depression. For this assessment, a translated version of the PHQ-9 was utilized to evaluate depressive symptoms experienced over the past 2 weeks. The scale consists of nine items, each rated on a four-point scale: "not at all" scored as 0, "several days" scored as 1, "more than half the day" scored as 2, and "nearly every day" scored as 3. In China, the PHQ-9 has been culturally adapted and validated, demonstrating a reliability coefficient of 0.86.[30] In addition, the Urdu version of the PHQ-9 used in Pakistan has a Cronbach's alpha of 0.91, further supporting its reliability in measuring depressive symptoms.[31]

The GAD-7 scale is a valid and reliable scale for screening the frequency of anxiety symptoms over the past 2 weeks. Each of the seven items is scored on a scale from 0 (not at all) to 3 (nearly every day), resulting in a total score that ranges from 0 to 21. Scores are interpreted as follows: 0 – 4 (minimal anxiety), 5 – 9 (mild anxiety), 10 – 14 (moderate anxiety), and 15 – 21 (severe anxiety). The reliability of GAD-7 was reported to be 0.79 – 0.91.[32] The GAD-7 was translated and validated for use in China, with adjustments made to ensure cultural relevance in measuring anxiety symptoms, yielding a Cronbach's alpha of 0.91.[33] In Pakistan, the Urdu version demonstrated a Cronbach's alpha of 0.92.[34]

2.3. Statistical analysis

Statistical tests for distribution and measurement were carried out on both healthy control and patient groups. These tests aimed to compare the mean scores between healthy controls and patients, as well as between patients from the two different countries. Specifically, analysis of variance was used to identify differences between variables, such as age, education, PSSS, P-subscale, S-subscale, PHQ-9, and GAD-7, with subsequent Tukey's *post hoc* analyses and correlation analyses. Results were presented in mean and standard deviation. In addition, a Chi-square test was conducted to evaluate differences between genders. All the statistical analyses were performed through IBM SPSS version 23.0 and R Studio.

2.4. Network estimate

Network analysis is a novel technique that can examine the dynamic and complex interrelationships among psychiatric symptoms, conceptualizing a specific disorder as an interacting cluster of interconnected symptoms rather than isolated entities. The nodes in network analysis represent psychiatric symptoms; the edges among the nodes represent the relationship between symptoms, with the activation spread through the network from one symptom to another.[35]

Network analysis was performed using the "qgraph" and "bootnet" packages in R programming. Model selection was based on the Extended Bayesian Information Criterion (EBIC), which identified more edges compared to other models.[36] The tuning parameter γ was set to 0.5 during network model selection to strike a balance between model simplicity and the detection of meaningful relationships between variables. We chose EBIC over alternatives such as AIC or the standard BIC because it is especially useful when working with complex psychological data that may include many weak or potentially misleading associations. EBIC applies an extra penalty that filters out weaker connections, which makes the final network easier to interpret and more likely to reflect true underlying patterns – an important consideration in psychological research.[37] During network analysis, strength, closeness, and betweenness were measured to examine node importance in the network.[38] These centralities were measured using the "qgraph" package, and normalized z-scores were plotted for each node. Strength measures the significance of each individual symptom in the network by summing the absolute edge weights of all direct connections between a particular node and other nodes. The frequency of a node that appears on all shortest paths to other nodes is known as "betweenness," and it reflects how important a symptom is as a "connector" to other symptoms. The reciprocal of the sum of a node's shortest path distances to all other nodes in a network is called "closeness," and it denotes how strongly one symptom is connected to other symptoms indirectly.[39]

2.5. Estimation of network stability

Previous studies tested the stability and accuracy of networks using the R package "bootnet." First, for the accuracy of estimating the edge weight, a non-parametric bootstrap procedure (1000 replicates; eight cores) was conducted to compute 95% confidence intervals (CIs) for the edge values. Bootstrap was then used to investigate significant differences between node strengths and edge weights. Finally, to investigate the stability of centrality, a case-dropping bootstrap (1000 replicates; eight cores) was conducted to determine the correlation stability coefficients. Correlation values were calculated between subsets and the original sample. The stability coefficient indicates the maximum number of cases that can be removed from the original sample set. For example, with 95% probability, the correlation coefficient between centrality in the case subset and the original network reached 0.7. Stability coefficients should not fall below 0.25, with values above 0.5 considered ideal.[37,39]

3. Results

3.1. Demographic characteristics

As displayed in Table 1, there were significant between-group differences in mean age and sex, with patients being older than healthy controls ($p<0.001$), and male patients were predominant ($p<0.001$). The number of years of education displayed a significant interaction between group and culture ($F = 9.27$; $p=0.002$), whereas the main effects of group ($F = 2.34$; $p=0.126$) and culture ($F = 0.529$; $p=0.467$) individually were not significant.

Analysis of the PSSS revealed a significant group and culture interaction effect ($F = 35.74$; $p<0.001$), indicating that the differences in psychosomatic symptoms between groups are influenced by cultural background. *Post hoc* tests further corroborated these findings. Specifically, a significant difference in PSSS total scores was found between the Chinese patient group (CHP) and Pakistani patient group (PKP), with the PKP group exhibiting higher levels of psychosomatic symptoms ($p<0.001$). In addition, significant differences were observed between the Chinese control group (CHC) and the Pakistani control group (PKC), where the CHC reported higher levels of psychosomatic symptoms ($p=0.001$).

Regarding the main effects of culture, both CHP and PKP exhibited significantly higher levels of psychosomatic symptoms than their respective control groups (CHC and PKC), with $p<0.001$ in both cases. This suggests that patients, regardless of culture, experience higher levels of psychosomatic

Table 1. Demographic information of all groups

Characteristic	Group[a]				Test							
	China		Pakistan		Group			Culture			Group and culture interaction		
	CHP (*n*=521)	CHC (*n*=300)	PKP (*n*=514)	PKC (*n*=298)	Main effect	*p*-value	Ad p	Main effect	*p*-value	Ad *p*-value	Main effect	*p*-value	Ad *p*-value
Age (years)	42.07 (16.8)	33.92 (13.04)	41.9 (13.13)	32.67 (6.81)	153.97	0.000	0.087	1.01	0.314	0.001	0.593	0.441	0.000
Sex (male, %)	37.8	41.3	42.60	23.60	0.041[b]	0.839	-	1.08[b]	0.298	-	-	-	-
Education (years)	16.51 (6.59)	15.03 (6.31)	15.73 (6.72)	16.12 (6.26)	2.34	0.126	0.001	0.529	0.467	0.000	9.27	0.002	0.006
PSSS	23.26 (13.04)	6.49 (8.19)	27.95 (81.37)	3.04 (1.38)	934.76	0.000	0.365	0.823	0.365	0.001	35.74	0.000	0.002
P-subscale	7.68 (5.14)	1.79 (2.8)	7.89 (5.01)	0.74 (0.90)	891.34	0.000	0.356	3.34	0.042	0.002	7.92	0.005	0.005
S-subscale	15.58 (9.34)	4.73 (5.92)	20.06 (13.67)	2.29 (1.21)	816.09	0.000	0.336	4.14	0.042	0.003	47.73	0.000	0.029
PHQ-9	10.65 (7.34)	2.19 (3.31)	13.18 (5.37)	1.85 (0.69)	1292.8	0.000	0.445	15.90	0.000	0.01	27.26	0.000	0.017
GAD-7	8.66 (6.29)	1.7 (3.0)	10.91 (4.79)	1.38 (2.24)	1235.38	0.000	0.434	10.48	0.001	0.006	37.86	0.000	0.023

Note: [a]Data is presented as mean (standard deviation), except for "Sex;" [b]χ^2 value.

Abbreviations: Ad: Adjusted; CHC: Chinese control group; CHP: Chinese patient group; GAD-7: Generalized anxiety disorder-7; P-subscale: Psychological subscale; PHQ-9: Patient health questionnaire-9; PKC: Pakistani control group; PKP: Pakistani patient group; PSSS: Psychosomatic symptom scale; S-subscale: Somatic subscale.

symptoms compared to control groups, but cultural variations still play a crucial role in the intensity of these symptoms, as evidenced by the significant interaction effect.

Further analysis of the factor scores of the PSSS, with comparative results of the psychological (P) and somatic (S) factor scores, is presented in the Appendix.

Analysis of the PHQ-9 revealed a significant main effect for groups (F = 1292.8; $p<0.001$), indicating that overall, patients have higher levels of depressive symptoms than control groups. There is also a significant main effect for culture (F = 15.90; $p<0.001$), suggesting that cultural differences influence the level of depressive symptoms. In addition, the significant group and culture interaction (F = 27.26; $p<0.001$) highlights that the relationship between group (patient vs. control) and depressive symptoms varies by culture.

Post hoc tests further corroborated these findings. A significant difference in PHQ-9 scores was found between CHP and PKP, with Pakistani patients reporting higher levels of depressive symptoms ($p<0.001$). However, no significant difference was found between CHC and PKC ($p=0.439$), indicating similar depressive symptoms between these two control groups. Cultural differences were significant when comparing CHP and CHC ($p<0.001$) and PKP and PKC ($p<0.001$), with both CHP and PKP reporting higher levels of depression than their respective control groups.

Analysis of the GAD-7 scores revealed a significant interaction between group and culture (F = 37.86; $p<0.001$), indicating that the relationship between anxiety symptoms and group (patients vs. controls) is influenced by cultural factors. *Post hoc* analyses displayed a significant difference in anxiety symptoms between the CHP and the PKP, with Pakistani patients exhibiting higher anxiety levels ($p<0.001$). However, no significant difference was found between CHC and PKC ($p=0.067$). In addition, both Chinese and Pakistani patients had significantly higher levels of anxiety symptoms compared to their respective control groups (CHC vs. CHP, $p<0.001$; PKC vs. PKP, $p<0.001$). This suggests that, while both patient groups exhibit elevated anxiety symptoms relative to controls, more Pakistani patients experience anxiety than their Chinese counterparts.

3.2. Network structure of PSSS

Network structure analysis of the PSSS in China and Pakistan revealed notable differences and patterns in symptom correlations. In China, the PSSS network is composed of 26 nodes with 167 out of 325 non-zero edges, indicating a substantial number of symptom connections. Key findings include a strong correlation between "depressed mood" and "no interest," as well as

strong edges between "sour regurgitation" and "nausea or vomiting," and between "dizziness" and "eye discomfort." These strong edges highlight clusters of symptoms that are closely related, suggesting that these symptom pairs may co-occur more frequently in Chinese patients.

In Pakistan, the PSSS network also consists of 26 nodes, but with slightly fewer non-zero edges (145/325). While many items in the Pakistani network also have strong edges, indicating robust symptom correlations, some items exhibit weaker connections. For example, weaker edges are observed between "discomfort of throat" and "sleep difficulty," as well as between "sour regurgitation" and "tiredness" as shown in Figure 1.

3.3. Centrality indices of the psychosomatic network structure in China and Pakistan

The centrality indices for the PSSS network structure in China and Pakistan revealed key symptoms that play central roles in the networks. In the Chinese PSSS, item p5 "depressed mood" stands out with the highest centrality (z-score = 2.0), followed by item p12 "nervousness" (z-score = 1.7) and item s24 "tiredness" (z-score = 1.5), indicating these symptoms are highly influential in the network. In terms of closeness, which reflects how quickly a symptom can influence others, item s24 "tiredness" (z-score = 2) is highly ranked, along with item p12 "nervousness" (z-score = 1.5) and item s26 "sleep difficulty" (z-score = 1.5). High betweenness, which suggests that a symptom acts as a bridge connecting different parts of the network, was observed in item s24 "tiredness" (z-score = 2), item s13 "dryness of mouth" (z-score = 1), and item s3 "burning or tight sensation" (z-score = 1).

In the Pakistani PSSS, item 14 "sour regurgitation" exhibited the highest strength (z-score = 1.6), followed by item s8 "discomfort of the throat" and item p11 "difficulty breathing," both with z-scores >1. Item 14 also reported high closeness and betweenness, suggesting its strong interconnectivity with other symptoms and a critical bridging role in the network. In addition, item p11 demonstrated high closeness (z-score >1), whereas item s26 "sleep difficulty" displayed high betweenness as shown in Figure 2.

3.4. Bootstrap CI

The edge weight bootstrap technique was applied to assess the accuracy of the estimated network, running at a 95% CI around the edge weights. The results, as depicted in Figure 3, indicate that the data lines and CIs were not excessively wide, suggesting reliable and stable edge estimates in the network. The close alignment of the original sample (red line) with the bootstrap estimates (black line), along with the gray-shaded 95% CI, confirms the robustness of the network structure. However, for edges with larger bootstrapped CIs, caution should be exercised when interpreting their strength and order, as these may indicate less stability or variability in those particular connections. Overall, the bootstrap CIs suggest that the network is generally well-estimated, but careful interpretation is needed for edges with wider intervals.

3.5. Stability of centrality indices based on the case-dropping subset bootstrap

The stability of the centrality indices was assessed using the case-dropping subset bootstrap technique, and the results indicated stable centrality values for both China and Pakistan, with values remaining around 0.5. In the graphs (Figure 4), the x-axis represents the percentage of the sample used at each step, while the y-axis displays the average correlations between the centrality indices from

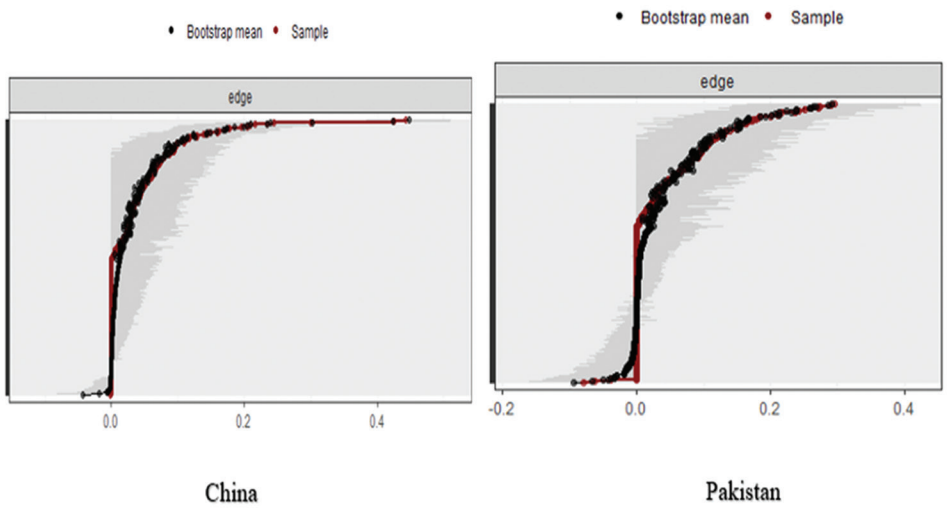

Figure 3. Bootstrap confidence interval

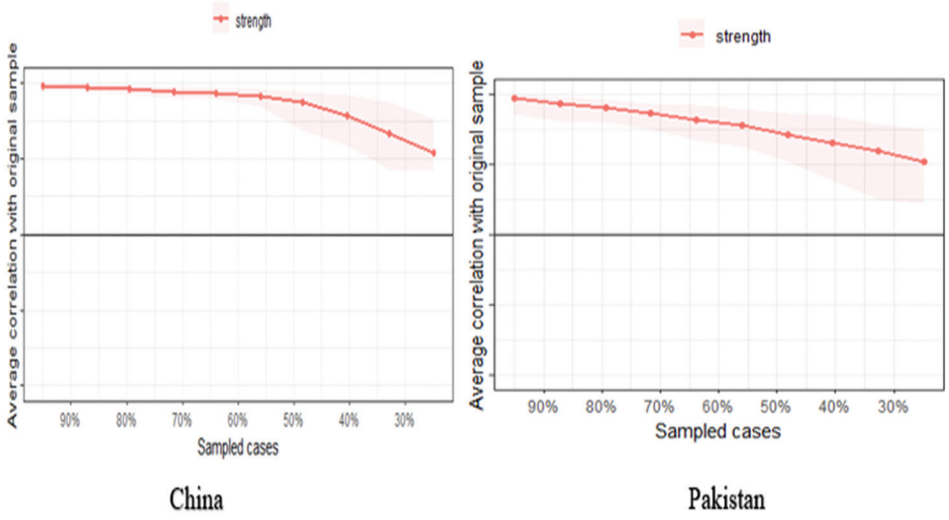

Figure 4. Stability of centrality indices based on the case-dropping subset bootstrap

the re-estimated networks and the original network. As increasing percentages of cases dropped, the stability of the centrality indices remained relatively high, reflecting a robust network structure.

At the start of the analysis, the CI (red) was relatively narrow, indicating precise estimates. However, as the sample size decreased, the CI gradually widened, suggesting increasing variability in the estimates as fewer cases were included. Despite this, the overall stability of the centrality indices remained strong, highlighting that the network's centrality estimates are reliable and resistant to changes even when subsets of the sample are dropped. This reinforces confidence in the robustness of the network and its centrality measures; however, wider CIs at lower sample sizes suggest that more caution is warranted when interpreting results with reduced data.

4. Discussion

This study sought to uncover the most prominent psychosomatic symptoms shared between China and Pakistan, highlighting the psychological and somatic experiences most frequently reported by individuals. Although many network studies have explored psychiatric symptoms within Asian populations, this research is the first to specifically investigate psychosomatic networks among Chinese and Pakistani patients.

The current study found some noteworthy links or correlations between somatic and psychological symptoms. The Chinese patients have a strong link or correlation between "cardiovascular symptoms" and "pulmonary symptoms" on the S-subscale. Chest tightness and breathlessness are the most common symptoms of emotional distress in this group. Chest tightness, pain, and palpitations are frequent symptoms in psychosomatic conditions, creating a diagnostic challenge for emergency and general practice providers when evaluating patients with these complaints.[40] As such, it is important for mental health providers to be aware of this connection.[41]

China and Pakistan are distinct countries with diverse cultures, lifestyles, languages, social norms, religions, and differing political, economic, and business conditions. In Pakistan, high socioeconomic pressure is strongly linked to elevated levels of depression, anxiety, and somatic symptoms, primarily due to the widespread prevalence of low socioeconomic status. Low socioeconomic status and financial crises exacerbate inequalities, material disadvantages, and poor educational opportunities, which collectively contribute to higher rates of depression, anxiety, and psychosomatic complaints. A study conducted by Patel *et al.*[42] highlights the elevated rates of mental illness among individuals in Pakistan, a low- and middle-income country.[42] This increase may be attributed to several factors, including the prevalence of natural disasters, armed conflict, and violence, which adversely impact mental well-being and development, with approximately 80% of mental health disorders occurring in middle- and low-income countries. In Pakistan, low educational attainment further exacerbates the risk of depression and anxiety, contributing significantly to the overall burden of common mental disorders, such as anxiety, somatoform disorders, and depression.[43]

Another reason for the discrepancy in mental health prevalence between the two countries could be the availability of mental health services. China has about 3000 mental health institutions that provide services to patients with mental health illnesses, including numerous psychiatric hospitals and a large number of specialized

psychiatrists.[44] In contrast, Pakistan has a severe shortage of mental health providers, with fewer than 344 psychiatrists available across the entire country. More than 90% of people with common mental disorders remain untreated. In 1993, China established a psychosomatic society that significantly contributed to psychosomatic medicine, focusing on the prevalence, diagnosis, treatment, and etiology of psychosomatic illnesses. The society has also published more than five journals dedicated to advancing research in this field.[45,46] Conversely, Pakistan lacks such facilities in the relevant field and would benefit from increased support.

There is significant literature that highlights how health and illness are differently perceived in different cultures.[47,48] Cultural beliefs profoundly influence practical outcomes, shaping individuals' decisions to pursue treatment, how they manage symptoms, and the extent of support they receive from their families and communities. It also determines where they seek assistance, whether from mental health professionals, primary care doctors, religious figures, or traditional healers, as well as the steps they take to access care and their overall treatment outcomes.[48,49] According to Helman,[50] cultures vary in how they explain the causes of illnesses, with some attributing it to personal factors, natural events, or social conditions. For example, certain cultures may link illness to superstitious or supernatural causes, such as spirit possession, the "evil eye," curses, or breaking cultural taboos. In these cases, healing is often entrusted to traditional healers, elders, or other influential community members. Furthermore, religion and spirituality significantly influence these perspectives, often viewing illness as tied to a broader spiritual or moral framework. As a result, solutions are typically sought within the boundaries of these cultural and spiritual systems.[51]

In some provinces of Pakistan, such as Sindh and Punjab, individuals with depression or other mental illnesses are treated with "magic" or amulets; in some cases, they are taken to grave sites and shrines for spiritual healing.[52] Moreover, limited awareness and cultural stigma surrounding mental illnesses often lead individuals to turn to spiritual healers for support. In addition, there is a significant shortage of specialized mental health professionals and facilities, coupled with insufficient financial resources and low mental health budgets.[53,54] For the entire population, there are fewer than 500 psychiatrists, only four major psychiatric hospitals, and 654 psychiatric units within general hospitals. This inadequate ratio results in a substantial treatment gap, leaving approximately 90% of individuals with common mental disorders without access to proper care.[55,56]

Numerous illnesses are recurrent, with a high likelihood of relapse.[57] Offering additional, tailored psychological interventions to address mild or early symptoms is essential for minimizing functional impairment and enhancing overall well-being.[58] However, despite the high prevalence of mental disorders, only about 20% of affected individuals have ever consulted a mental health professional. In China, there is also a shortage of mental health professionals, particularly trained social workers and psychologists. The financial burden of psychological counseling is further compounded by inadequate coverage under medical insurance plans.[59,60] In comparison to Pakistan, China has significantly more developed mental health facilities.

Across the United States of America (USA), Asians and Asian Americans (collectively referred to as Asians) exhibit the lowest rate of mental health service usage (25%) compared to other racial and ethnic groups, who utilize these services at rates of 39–52%. This disparity persists despite high levels of depression, anxiety, and suicidal thoughts within the Asian community.[61,62] The COVID-19 pandemic has further exacerbated mental health challenges among Asian populations, leading to significant increases in mental health concerns.[63] Between 2019 and 2020, diagnoses of depression among Asians in the USA rose by 104%, while anxiety disorders increased by 97%.[64] In 2021, over 40% of Asian individuals reported experiencing mental health symptoms,[65] and one in six Asian adults reported being targeted by hate crimes or incidents.[66]

Stigma, defined as a social process that excludes individuals from full societal acceptance, is deeply rooted in cultural norms and values and varies across cultural groups.[67,68] Racial and ethnic differences in stigma levels are well-documented, including the endorsement of negative stereotypes about individuals with mental disorders (e.g., perceiving them as dangerous) and a desire for social distance.[69,70] Asian Americans report higher stigma levels than other groups, including White individuals, potentially due to concerns about bringing shame to their families.[70-72]

Elevated stigma among Asian Americans impacts their help-seeking attitudes, likely hindering the decision-making process.[70] Loya *et al.*[73] found that stigma differences accounted for variations in help-seeking attitudes between White and South Asian American college students. Although Asian Americans generally report higher stigma levels than White individuals, the extent and causes of this disparity vary across Asian American subgroups. For instance, Chinese Americans may avoid mental health services due to perceived shame rather than skepticism toward Western medicine,[74] while cultural mistrust contributes to negative help-seeking attitudes among Filipino Americans.[75]

This study presented a cross-cultural clinical comparison of psychosomatics, depression, and anxiety between China and Pakistan. Due to the unavailability of an updated Urdu version, we utilized older versions of the PHQ and GAD scales for data collection. In addition, cultural and genetic factors, both of which may influence the prevalence and expression of psychosomatic symptoms, depression, and anxiety, were not included in the current analysis. A slight difference in the average age between the two groups was also observed, which may have had an impact on the findings.

5. Conclusion

Psychosomatic symptoms, depression, and anxiety were significantly different between the participants from China and Pakistan, with the Pakistani group displaying markedly higher symptom levels. The network analysis uncovered unique patterns of interconnected symptoms, illuminating the complex interplay between emotional and physical health as influenced by cultural factors. These findings emphasize the dynamic interplay between mental and physical well-being across diverse populations, sparking the need for deeper exploration in these countries and other Asian populations to uncover whether similar symptom patterns prevail.

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Conflict of interest

Yonggui Yuan is the Editor-in-Chief and Wenhao Jiang is the Associate Editor of this journal, but were not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Yonggui Yuan, Wenhao Jiang, S. Mudasser Shah
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Investigation: S. Mudasser Shah
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Writing–review & editing: Yonggui Yuang, Chand Taneja, Wei Xu, Sun Taipeng, Chen Gang, Tianyu Wang, Wenhao Jiang

Ethics approval and consent to participate

The study was approved by the ethical committee of Zhongda Hospital at the Southeast University, Nanjing, Jiangsu, China (registration no. 2021ZDSYLL347-P01). All participants signed an informed consent form before participation.

Consent for publication

The informed consent forms were completed and signed by all participants in our study.

Availability of data

Data will be available upon request from the corresponding authors.

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Appendix

The psychosomatic subscale (P-subscale) indicated a significant difference in group and culture interactions (F = 7.92; p=0.005). *Post hoc* analysis revealed that in "group," the Chinese patient group (CHP) and Pakistani patient group (PKP) displayed no significant difference (p=0.414), while the Chinese control group (CHC) and the Pakistani control group (PKC) displayed a significant difference (p=0.004). CHC reported higher levels of psychological symptoms compared to PKC. In "culture," the *post hoc* analysis revealed that CHP versus CHC (p<0.001) and PKP versus PKC (p<0.001) displayed significant differences, suggesting that in both countries, more patients exhibited psychological symptoms compared to the control group.

The somatic subscale (S-subscale) indicated a significant difference in the main effect of group and culture interactions (F = 47.73; p<0.001). The *post hoc* test revealed that in "group," CHP versus PKP (p<0.001) and CHC versus PKC (p<0.001) displayed a significant difference. In addition, more Pakistani patients have somatic symptoms than Chinese patients. The *post hoc* analysis for "culture" revealed a significant difference for CHP versus CHC (p<0.001) and PKP versus PKC (p<0.001). In both countries, more patients exhibit somatic symptoms compared to the control groups (Table 1).

ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Psychological burden and burnout among midwives: An epidemiological study in Thessaly, Greece

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Abstract

The COVID-19 pandemic has had a profound psychological impact on healthcare workers worldwide, including midwives across various levels of the healthcare system. This study aims to evaluate the psychological strain experienced by midwives in the region of Thessaly, Greece, due to the pandemic. Specifically, it examines levels of burnout while considering perceived stress, depression, and psychological resilience, as well as demographic, socio-economic, and occupational factors. This epidemiological study explores the extent of psychological distress among midwives in Thessaly during the COVID-19 crisis. Data collection was conducted between February and March 2021, involving 102 midwives, with a primary focus on burnout symptoms. Data were collected from three electronic databases: PubMed, MEDLINE, and PsycINFO. Information was gathered through a structured questionnaire covering sociodemographic and professional characteristics, alongside validated assessment tools, including the Spielberger State-Trait Anxiety Inventory, the Connor–Davidson Resilience Scale, the Beck depression inventory, and the Copenhagen Burnout Inventory. Statistical analysis was conducted using multifactorial linear regression to identify factors influencing midwives' mental health during the pandemic. Midwives experiencing high stress and burnout had an increased risk of depression, whereas psychological resilience was identified as a crucial protective factor against depressive symptoms. Midwives in Thessaly, Greece, have faced substantial psychological distress, with their overall mental well-being significantly impacted by the COVID-19 pandemic. These findings emphasize the need for targeted psychological support and preventive interventions for midwives, particularly in ongoing or future public health crises.

Keywords: Pandemic; Coronavirus; COVID-19; Midwives; Burnout; Psychological burden; Mental health

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1. Introduction

In December 2019, a new and undoubtedly dangerous respiratory disease emerged in Wuhan, the capital of Hubei province in China. Chinese authorities alerted the World Health Organization (WHO) about an unusual form of pneumonia caused by an unidentified virus, suspected to be linked to the city's wet market.[1] This disease was later officially named COVID-19. Within 4 months, the virus had spread throughout China and internationally, despite continuous warnings and recommendations from the WHO regarding containment and prevention measures.[2,3]

The pandemic presented numerous challenges, including inadequate planning, insufficient preparedness, and poor organization by local governments in managing healthcare systems. In addition, the failure to ensure adequate supplies of essential medical equipment for protecting healthcare workers exacerbated the crisis. These shortcomings led to ethical dilemmas regarding public health responses and raised bioethical concerns among healthcare professionals.[2]

The rapid and extensive spread of the novel "COVID-19" became one of the most pressing global health concerns.[4] This crisis had a profound negative impact on the mental well-being of frontline healthcare professionals, who played a vital role in combating the pandemic.[5,6] Midwives, in particular, continued to provide essential care throughout this period, with many referring to them as heroes.[2]

Psychological distress is characterized by intense and prolonged stress that leads to both physical and emotional strain, with social and financial repercussions for those affected.[7] Healthcare professionals frequently experience chronic exhaustion in their workplaces due to their responsibility for patient care.[8] Mental resilience is a key factor in helping them adapt to and endure the crisis with reduced stress, anxiety, emotional exhaustion, and depressive symptoms.[9]

Midwifery holds a unique and respected place in healthcare, offering compassionate and individualized care to individuals, families, and communities. A midwife's role extends beyond assisting in childbirth; they also provide support and guidance to women during one of their lives' most important and transformative phases. In addition, midwives play a crucial role in advising on various health-related aspects of childbirth and neonatal care. Their contributions are vital to the continuation, protection, and well-being of the human population.[9]

The exceptional nature of the COVID-19 pandemic and its substantial psychological toll on the general population, particularly on midwives, prompted the need for this study. The full extent of the pandemic's impact on the mental health of professionals working in obstetrics and gynecology remains unclear. While research in this area has increased in recent years, most studies focus on medical and nursing personnel, with significantly fewer studies examining the specific psychological burden on midwives. The primary aim of this study was to explore and assess the psychological burden of burnout experienced by midwives in the Region of Thessaly, Greece, due to the COVID-19 pandemic. This included evaluating levels of occupational burnout while considering stress, depression, and psychological resilience, as well as demographic, socio-economic, and workplace factors that may influence these mental health outcomes. Furthermore, the study sought to identify potential risk factors contributing to these conditions. The findings are expected to serve as a valuable resource for developing strategies to support the mental well-being of midwives during the ongoing health crisis.

2. Materials and methods

2.1. Study population, methods, and ethical considerations

This study is an epidemiological survey focusing on the psychological burden experienced by midwives in the Thessaly region of Greece due to the COVID-19 pandemic. Data collection and literature review were conducted between February and March 2021. The research is observational, meaning the researcher did not intervene or influence the results but simply observed, aiming to identify correlations between dependent and independent variables.[10]

The literature review began with a focus on defining key concepts such as anxiety, stress, burnout, depression, and psychological resilience in the context of midwives and healthcare workers on the frontlines of the COVID-19 pandemic. The search was conducted through databases such as PubMed, MEDLINE, and PsycINFO, using keyword combinations related to COVID-19 (e.g., "coronavirus" and "COVID-19"), psychological burden (e.g., "depression" and "stress"), and terms like "COVID-19" in conjunction with "mental health" or "midwives."

Approval for conducting the research was obtained from the Scientific Council of the Midwives Association of Thessaly, allowing the questionnaire to be distributed to its members via email. Due to the limitations of in-person data collection during the pandemic, quantitative data were gathered through structured questionnaires through Google Forms, which complies with privacy standards to ensure data protection. The study did not request any personal or institutional information. Participants were

informed about data confidentiality, the purpose of the research, their voluntary participation, and their right to withdraw. The study included 102 midwives who confirmed their consent to participate by selecting the "Agree" option. The research focused on identifying symptoms of anxiety, depression, burnout, and psychological resilience among the participants.

2.2. Research tools

The questionnaire consisted of five sections and included the following:

(i) Demographic and professional characteristics: Information about the respondents' gender, age, marital and financial status, number of children, history of chronic illness, general health status, education level, and professional details such as the institution and healthcare level they work in, years of experience, and COVID-19-related questions. The content was developed based on a review of relevant literature.

(ii) Spielberger State-Trait Anxiety Inventory (STAI): This questionnaire consists of 40 items and assesses anxiety both as a personality trait and as a situational state.[11] The state anxiety scale evaluates anxiety as a temporary emotional state, while the trait anxiety scale measures the individual's general tendency to experience anxiety. The inventory was administered to all participants in a controlled setting. Each scale includes 20 items rated on a 4-point Likert scale, with higher scores indicating greater anxiety levels.

(iii) Connor–Davidson Resilience Scale: This tool measures psychological resilience based on key factors such as trust in personal instincts, tolerance for negative experiences, personal competence, self-efficacy, sense of control, a positive attitude toward change, spiritual influences, and secure relationships.[12]

(iv) Beck depression inventory: This widely used tool assesses the cognitive, behavioral, and somatic manifestations of depression, along with its severity over the previous week. It is recognized as one of the most commonly used tools for depression assessment globally.[13]

(v) Copenhagen burnout inventory: This tool evaluates burnout across three subscales: (a) personal burnout, (b) work-related burnout, and (c) client-related burnout. It has demonstrated adequate construct validity and satisfactory reliability (Cronbach's $\alpha = 0.844$).[14]

2.3. Statistical analysis

The distributions of quantitative variables were assessed for normality using the Kolmogorov–Smirnov test. Descriptive statistics were reported as means and standard deviations (SDs) for normally distributed variables. For non-normally distributed variables, medians and interquartile ranges were used. Qualitative variables were described using absolute (n) and relative (%) frequencies. The non-parametric Mann–Whitney U test or the parametric Student's t-test was employed to compare quantitative variables between two groups, depending on the distribution. The non-parametric Kruskal–Wallis test or the parametric analysis of variance was applied for comparisons involving more than two groups. The Bonferroni correction was applied to adjust for multiple comparisons and control the risk of type I error, with the significance level set at $0.05/k$, where k represents the number of comparisons. Pearson's or Spearman's correlation coefficient (r) was used to examine relationships between two quantitative variables. Pearson's correlation was the primary method applied, with Spearman's correlation employed only when the assumption of normality was not met, as verified through appropriate diagnostics. The strength of correlation was categorized as low ($r = 0.1 - 0.3$), moderate ($r = 0.31 - 0.5$), and high ($r > 0.5$). To identify independent factors associated with the outcome measures, linear regression analysis was performed using a stepwise selection process, yielding dependency coefficients (β) and their standard errors. For the depression and resilience scales, logarithmic transformations were applied in the regression analysis. The internal consistency of the distributed questionnaire was assessed using Cronbach's α coefficient. All statistical tests were two-sided, with significance set at $p<0.05$. Analyses were carried out using SPSS version 22.0 (IBM Corp., USA).

3. Results

The sample consisted of 102 midwives. The demographic and occupational characteristics are presented in Table 1.

A total of 54.9% of participants were 35 years old or younger. The majority (84.3%) were married, and 82.4% reported having children. In addition, 14.7% of participants reported having a chronic disease, while 88.2% rated their health as good or very good. A total of 82.4% of the sample reported a low to moderate financial status, and two-thirds of the participants (66.7%) held an undergraduate degree. Most participants (69.6%) worked in the public healthcare sector, with 49.0% employed at the primary healthcare level. In addition, 52.0% had 10 years or less of work experience, and 23.5% worked in units treating COVID-19 patients. Table 2 presents findings related to the pandemic and the associated stress reported by participants.

A total of 79.4% of participants reported experiencing stress about contracting COVID-19 due to their work, and

Table 1. Demographic and occupational characteristics of 102 midwives

Characteristic	*n*	%
Age (years)		
≤35	56	54.9
≥36	46	45.1
Marital status		
Married	86	84.3
Single/divorced	16	15.7
Has children		
No	18	17.6
Yes	84	82.4
Chronic disease history		
No	87	85.3
Yes	15	14.7
Health status		
Good/very good	90	88.2
Poor/moderate	12	11.8
Financial status		
High	18	17.6
Low/moderate	84	82.4
Education level		
Undergraduate	68	66.7
Postgraduate	33	32.4
Doctorate	1	1.0
Workplace sector		
Private	31	30.4
Public	71	69.6
Healthcare level		
Primary	50	49.0
Secondary	34	33.3
Tertiary	18	17.6
Years of work experience		
≤10	53	52.0
≥11	49	48.0
Treatment of COVID-19 patients at the workplace		
No	78	76.5
Yes	24	23.5

90.2% were concerned about transmitting the virus to a family member. In addition, 37.3% stated that they spent less time with patients than before the pandemic, while 15.7% reported that knowing that pregnant women were tested for COVID-19 before visiting them did not reduce their stress.

Table 2. Pandemic-related stress reported by midwives in the sample

Question	Response	*n*	%
Are you stressed about contracting COVID-19 due to your job?	No	21	20.6
	Yes	81	79.4
Are you stressed about transmitting COVID-19 to a family member due to your job?	No	10	9.8
	Yes	92	90.2
Do you spend less time with patients due to the pandemic?	No	64	62.7
	Yes	38	37.3
Do you feel less stressed knowing that pregnant women are tested for COVID-19 before seeing you?	No	16	15.7
	Yes	86	84.3

3.1. Resilience scale

Table 3 shows the resilience scale scores of the participants. Higher scores indicate greater resilience.

The resilience scale scores ranged from 7 to 100, with a mean score of 70.3 (SD = 18.3). The Cronbach's α coefficient of 0.96 indicates excellent reliability of the scale.

3.2. Depression scale

Table 4 presents the participants' scores on the Beck Depression Inventory scale. Higher scores indicate more severe depressive symptoms.

The depression scores ranged from 0 to 61, with a mean score of 9.7 (SD = 11.6). The Cronbach's α coefficient was above the acceptable threshold (0.7), indicating good reliability of the scale. Table 5 presents the depression levels of the participants, showing that 63% of participants showed no signs of depression and 15% experienced minimal depressive symptoms.

3.3. State-Trait Anxiety Inventory

Participants' anxiety levels were assessed using STAI, a widely used measure of situational (state) and general (trait) anxiety. Descriptive statistics and internal consistency values (Cronbach's α) for the scales are shown in Table 6.

Table 6 presents the summary statistics for participants' scores on STAI, including the minimum, maximum, mean, and SD for both the state and trait anxiety scales, along with the internal consistency coefficients (Cronbach's α). The scores on the state anxiety scale ranged from 23 to 73, with a mean value of 42.5 and a SD value of 11.3. Similarly, scores on the trait anxiety scale ranged from 20 to 76, with a mean value of 41.9 and a SD value of 11.7. Both scales demonstrated high internal consistency, with Cronbach's α values of 0.92 and 0.93 for the state and trait anxiety scales, respectively, indicating strong reliability.

Table 3. Resilience scale scores of the participants

Scale	Minimum score	Maximum score	Mean (standard deviation)	Median (interquartile range)	Cronbach's α
Resilience scale	7.00	100.00	70.3 (18.3)	73 (62 – 83.5)	0.96

Table 4. Participants' scores on the beck depression inventory

Scale	Minimum core	Maximum score	Mean (standard deviation)	Median (interquartile range)	Cronbach's α
Depression scale	0.0	61.0	9.7 (11.6)	6 (1 – 14.5)	0.95

Table 5. The depression levels of the participants

Depression level	*n*	%
No depression	63	63.0
Minimal depression	15	15.0
Mild depression	11	11.0
Moderate depression	11	11.0

Table 6. Descriptive statistics and reliability for the State-Trait Anxiety Inventory

Scale	Score range	Mean (standard deviation)	Cronbach's α
State anxiety scale	23 – 73	42.5 (11.3)	0.92
Trait anxiety scale	20 – 76	41.9 (11.7)	0.93

3.4. Copenhagen burnout inventory: Occupational burnout scale

Table 7 presents the participants' scores across the dimensions of the occupational burnout scale. High values indicate high levels of occupational burnout.

The mean score for the personal burnout dimension was 54.1 (SD = 20.6), work-related burnout was 44.6 (SD = 22.2), and patient-related burnout was 36.1 (SD = 22.6). The Cronbach's α reliability coefficients exceeded the acceptable threshold (0.7), indicating satisfactory reliability of the scale.

3.4.1. Conceptual relationships between occupational burnout and measures of resilience, depression, and anxiety

Table 8 illustrates the expected relationships between occupational burnout dimensions (personal, work-related, and patient-related) and psychological variables (resilience, depression, state anxiety, and trait anxiety). In this study, it was hypothesized that the dimensions of occupational burnout would be significantly related to measures of resilience, depression, and anxiety. Based on existing literature,[15-17] we expected that higher resilience would correlate with lower levels of burnout, as resilient individuals tend to manage stress more effectively. Conversely, we anticipated that higher depression, state anxiety, and trait anxiety would be associated with higher levels of occupational burnout. These conceptual relationships are illustrated in Table 8, where we outline the expected direction of these associations.

The table illustrates expected trends based on existing literature. Higher resilience is anticipated to correlate with lower burnout, while greater depression, state anxiety, and trait anxiety are expected to correlate with higher levels of occupational burnout. Table 9 shows the scores of the participants on the dimensions of professional burnout according to their demographic and occupational characteristics.

Significantly higher burnout was observed in all three dimensions for participants with poor/average health status. The work-related burnout score differed significantly based on the participants' work level. After Bonferroni correction, it was found that participants working at the tertiary level reported significantly more burnout compared to those working at the primary level (p=0.011). Table 10 shows the scores of participants in the dimensions of professional burnout according to factors related to the pandemic.

Participants who spent less time with patients compared to before the pandemic reported significantly higher levels of professional burnout in all three dimensions. The score on the "work-related burnout" scale was significantly higher for participants who were anxious about transmitting COVID-19 to a family member. The score on the "burnout related to patients" dimension was significantly higher among participants who did not feel less anxious about pregnant women being tested for COVID-19 before their visits. Subsequent analyses of multivariate linear regression were conducted, with burnout scores and independent variables, including the demographic and occupational factors of the participants, pandemic-related factors, and the resilience, temporary, and chronic anxiety scores, serving as dependent variables. The analyses were performed using a stepwise inclusion–exclusion method.

Table 7. The participants' scores across the dimensions of the occupational burnout scale

Dimension	Minimum score	Maximum score	Mean score (standard deviation)	Cronbach's α
Personal burnout	4.17	100.00	54.1 (20.6)	0.94
Work-related burnout	0.00	100.00	44.6 (22.2)	0.84
Patient-related burnout	0.00	100.00	36.1 (22.6)	0.91

Table 8. Conceptual relationships between occupational burnout and measures of resilience, depression, and anxiety

Scale	Personal burnout	Work-related burnout	Patient-related burnout
Resilience scale	Lower burnout	Lower burnout	Lower burnout
Depression scale	Higher burnout	Higher burnout	Higher burnout
State anxiety scale	Higher burnout	Higher burnout	Higher burnout
Trait anxiety scale	Higher burnout	Higher burnout	Higher burnout

Table 11 shows the results with the personal burnout dimension as the dependent variable.

The trait anxiety and depression scales of the participants, and whether they spent less time with patients compared to before the pandemic, were found to be independently associated with the score on the "personal burnout" dimension. Specifically, participants who spent less time with patients compared to before the pandemic had a higher score of 10.12, indicating more personal burnout. The more depressive symptoms participants experienced, the higher their level of personal burnout. Personal burnout increased with trait-anxiety symptoms. Table 12 shows the results with work-related burnout dimension as the dependent variable.

The resilience and depression scales of the participants, as well as whether they spent less time with patients compared to before the pandemic, were found to be independently related to the score in the "work-related burnout" dimension. Notably, participants who spent less time with patients compared to before the pandemic had a higher score of 12.22, indicating more work-related burnout. The more depressive symptoms the participants experienced, the higher the level of work-related burnout they faced. Work-related burnout increased with depression and decreased with resilience. Table 13 shows the results with patient-related burnout as the dependent variable.

The resilience and depression scales of the participants, whether they spent less time with patients compared to before the pandemic, and whether they felt less anxious that pregnant women were tested for COVID-19 before visiting them, were found to be independently associated with the score in the "patient-related burnout" dimension. Particularly, participants who spent less time with patients compared to before the pandemic had a higher score of 8.67, indicating greater patient-related burnout. Participants who felt less anxious about pregnant women being tested for COVID-19 before visiting them had a lower score of 11.86 points, indicating greater patient-related burnout. Patient-related burnout increased with depression and decreased with patient resilience.

4. Discussion

This study investigated the impact of the COVID-19 pandemic on the mental health of midwives in the Thessaly region. The key findings demonstrated that 79.4% of participants reported anxiety about contracting COVID-19 due to their work, while 90.2% of them were concerned about transmitting the virus to a family member because of their job. These findings closely mirror the findings by Lai *et al.*[3] Moreover, 37.3% of participants noted that they spent less time with patients compared to before the pandemic, which contrasts with the findings of Lai *et al.*,[3] who observed that the quality of healthcare services provided by healthcare workers remained unchanged. Despite the implementation of COVID-19 testing for pregnant women before their visits, 15.7% of participants reported not feeling less anxious. In addition, 63.0% of participants did not exhibit any signs of depression, while 15.0% of them showed mild depression. This is significant when considering the average mental health burden in frontline healthcare workers, compared to the lower depression rates found in other countries, as reported in studies from Iran, China, India, and Italy.[8]

Unlike findings from Talevi *et al.*,[5] where high rates of depression and anxiety were associated with gender and younger age, these trends were not observed in the present study. The overall findings suggest that midwives in Thessaly showed a slight concern for their psychological well-being during the pandemic, with notable anxiety related to the risks of infection and transmission. However, the reported depression rates were lower compared to the rates found in other countries, indicating a relatively more resilient psychological response among the midwives in

Table 9. Participants' scores on the dimensions of professional burnout according to demographic and occupational characteristics

Parameters	Personal burnout	Student's *t*-test	Work-related burnout	Student's *t*-test	Burnout related to patients	Student's *t*-test
Age (years)						
≤35	51.2 (19.2)	0.124	43.7 (20.7)	0.643	35.4 (21.1)	0.737
≥36	57.5 (21.8)		45.7 (24)		37 (24.6)	
Marital status						
Married	54 (20.3)	0.899	44.6 (22)	0.994	35.2 (22.5)	0.336
Single/divorced	54.7 (22.8)		44.6 (24)		41.1 (23.3)	
Has children						
No	54.2 (20.5)	0.985	44.6 (22.9)	0.994	38.9 (20)	0.570
Yes	54.1 (20.7)		44.6 (22.2)		35.5 (23.3)	
Chronic illness history						
No	53.6 (19.7)	0.601	43.2 (21.4)	0.130	35.2 (21.9)	0.331
Yes	56.7 (25.9)		52.6 (25.5)		41.4 (26.7)	
Health status						
Good/very good	51.8 (18.8)	0.002*	41.7 (20.7)	<0.001*	33.9 (20.9)	0.006*
Poor/moderate	71.2 (25.5)		65.8 (21.7)		52.8 (28.6)	
Economic status						
High	57.2 (24.3)	0.484	49 (21.6)	0.355	43.8 (21.7)	0.115
Low/moderate	53.4 (19.8)		43.6 (22.3)		34.5 (22.6)	
Education level						
Undergraduate education	53.2 (19.5)	0.531	43.1 (21.1)	0.343	34.3 (22.5)	0.260
Postgraduate/doctorate	55.9 (22.8)		47.6 (24.4)		39.8 (22.8)	
Healthcare provider						
Private	50 (21.5)	0.185	43 (21.2)	0.624	35.8 (23.7)	0.913
Public	55.9 (20.1)		45.3 (22.7)		36.3 (22.3)	
Work health level						
Primary	51.7 (15.6)	0.114+	38.8 (19.1)	0.012+*	33.1 (19.9)	0.432+
Secondary	52.6 (22.6)		46.6 (22.4)		38.6 (22.9)	
Tertiary	63.2 (26.4)		56.3 (25.3)		39.6 (28.7)	
Years of work experience						
≤10	51.3 (19.8)	0.170	42.8 (22.3)	0.405	36 (20.9)	0.966
≥11	57 (21.2)		46.5 (22.1)		36.2 (24.5)	
Are patients with COVID-19 being hospitalized in the healthcare unit where you work?						
No	52.6 (18.5)	0.211	42.2 (21)	0.053	35.9 (21.5)	0.833
Yes	58.7 (26.1)		52.2 (24.4)		37 (26.5)	

Notes: Data are presented as mean (standard deviation); * indicates statistically significant values ($p<0.05$); + represents analysis of variance as the statistical tool used.

Thessaly. The findings also highlight the unique pressures faced by midwives, given their high morbidity risk due to close patient contact and their involvement in both obstetric and gynecological care, as well as pandemic-related services.

Significant associations were found between all dimensions of the burnout and the resilience, anxiety, and depression scales. Specifically, higher resilience levels were linked to lower levels of professional burnout, as observed in the study by Yörük and Güle.[8] In addition, increased

Table 10. Participants' scores in the dimensions of professional burnout according to pandemic-related factors

Questions	Answer	Personal burnout	Student's *t*-test	Work-related burnout	Student's *t*-test	Burnout related to patients	Student's *t*-test
Do you feel anxious about contracting COVID-19 due to your work?	No	46.3 (15.3)	0.057	36.3 (18)	0.059	27.9 (19.5)	0.070
	Yes	56 (21.3)		46.7 (22.7)		38.2 (23)	
Does the thought of transmitting COVID-19 to a family member due to your work make you anxious?	No	41.7 (14.1)	0.058	29 (21.8)	0.026*	25.5 (28.4)	0.139
	Yes	55.3 (20.8)		46.2 (21.7)		37.2 (21.9)	
Do you spend less time with the patients now compared to before the pandemic?	No	49.1 (20.7)	0.002*	38.4 (20.8)	<0.001*	31.2 (21.2)	0.005*
	Yes	62.3 (17.8)		54.7 (20.8)		44.2 (22.9)	
Do you feel less anxious when pregnant women are tested for COVID-19 before they visit you?	No	61.1 (24.4)	0.153	51.7 (29.4)	0.183	51.1 (26.9)	0.005*
	Yes	52.8 (19.7)		43.4 (20.6)		33.5 (20.9)	

Notes: Data are presented as mean (standard deviation); * indicates statistically significant values (p<0.05).

Table 11. Stepwise inclusion–exclusion method with personal burnout as the dependent variable

Parameter	β	SE	*p*-value
Trait anxiety scale	0.49	0.19	0.011*
Do you spend less time with patients compared to before the pandemic?			
No (reference)	—	—	—
Yes	10.12	3.65	0.007*
Depression scale	0.44	0.19	0.020*

Notes: The independent variables include the demographic and occupational factors of the participants, pandemic-related factors, depression, as well as temporary and chronic anxiety scores. Health status has been clarified as part of pandemic-related factors; * indicates statistically significant values (p<0.05).
Abbreviations: β: Coefficient of dependence; SE: Standard error of the coefficient.

Table 12. Stepwise inclusion–exclusion method with work-related burnout as the dependent variable

Parameter	β	SE	*p*
Resilience scale	−0.30	0.12	0.020*
Due to the pandemic, do you spend less time with the patient compared to before the pandemic?			
No (reference)	—	—	—
Yes	12.22	3.90	0.002*
Depression scale	0.58	0.19	0.003*

Notes: The independent variables include the demographic and occupational factors of the participants, pandemic-related factors, depression, as well as temporary and chronic anxiety scores; * indicates statistically significant values (p<0.05).
Abbreviations: β: Coefficient of dependence; SE: Standard error of the coefficient.

depressive symptoms and permanent or temporary anxiety symptoms[18] were significantly associated with high levels of professional burnout, consistent with findings from

Table 13. Stepwise inclusion–exclusion method with patient-related burnout as the dependent variable

Parameter	β	SE	*p*
Resilience scale	−0.44	0.13	0.001*
Do you feel less anxious that pregnant women are tested for COVID-19 before visiting you?			
No (reference)	—	—	—
Yes	−11.86	5.28	0.027*
Due to the pandemic, do you spend less time with the patient compared to before the pandemic?			
No (reference)	—	—	—
Yes	8.67	3.96	0.031*
Depression scale	0.38	0.19	0.046*

Notes: The independent variables include the demographic and occupational factors of the participants, pandemic-related factors, depression, as well as temporary and chronic anxiety scores; * indicates statistically significant values (p<0.05).
Abbreviations: β: Coefficient of dependence; SE: Standard error of the coefficient.

the study of Aksoy and Koçak.[19] Participants with poor or moderate health status and those who spent less time with patients compared to before the pandemic exhibited higher burnout levels across all three dimensions: Personal burnout, work-related burnout, and patient-related burnout. Moreover, work-related burnout scores varied significantly according to participants' job level. For instance, midwives working in tertiary healthcare settings experienced significantly higher exhaustion levels compared to those in primary healthcare settings (p=0.011), as indicated in the studies by Talevi *et al.*,[5] Huang *et al.*[20] on tertiary healthcare institutions, and Yörük and Güle.[8] Participants who feared transmitting COVID-19 to a family member exhibited high work-related burnout and patient-related burnout. Midwives who spent less time with patients and reported higher depressive symptoms experienced greater work-related

burnout. However, increased resilience was associated with lower levels of work-related burnout. Midwives who felt less anxious about pregnant women being tested for COVID-19 before their visits exhibited high levels of patient-related burnout. Patient-related burnout increased with depressive symptoms, while it decreased as resilience increased. Personal burnout was recorded among midwives who spent less time with patients before the pandemic, with an increase proportional to depressive and persistent anxiety symptoms.

Multivariate linear regression revealed that depression and reduced patient interaction time were significant predictors of all three burnout subscales, while resilience was a protective factor in both work-related and patient-related burnout.

4.1. Implications of the study

Midwives with high levels of anxiety and professional burnout were at greater risk of depression, while psychological resilience emerged as a significant protective factor against depressive symptoms. Individuals with high resilience reported few depressive symptoms and anxiety. Furthermore, midwives who spent less time with patients than before the pandemic were more likely to experience burnout related to patient care compared to those in the primary sector. Healthcare workers in tertiary healthcare structures were more vulnerable to the psychological effects of the pandemic compared to those in primary healthcare settings.

To support midwives, interventions focusing on building resilience and moral courage are essential. It is crucial to protect healthcare workers as part of the broader public health efforts in combating the pandemic. Targeted interventions aimed at enhancing mental well-being and psychological resilience, such as ongoing education and behavioral therapies, are necessary. Healthcare workers with greater adaptability, mental flexibility, and a sense of humor tend to handle stressful situations well, making these traits key to developing strong psychological resilience. Health sector interventions should be incorporated into emergency preparedness and response plans, focusing on three main areas: (i) the establishment of multidisciplinary mental health teams, (ii) a continuous communication with updates on the pandemic, and (iii) the development of psychological counseling services through telemedicine or peer support groups to share experiences.

Special attention should be given to vulnerable midwives with poor or moderate health conditions, providing them with targeted psychological interventions. In addition, midwives could benefit from regular monitoring of their mental health, training on managing uncooperative patients, and prioritizing self-care, including adequate time for eating, sleeping, and rejuvenation.

4.2. Limitations of the study

This study has various limitations that should be considered when interpreting its results. The limitation lies in the cross-sectional nature of the study, as it only provided insights into the midwives' mental health at 1 time point. Furthermore, data were collected through self-reports, which may introduce biases. Participants could have underreported or overreported their mental health symptoms, affecting the reliability of the findings. In addition, the study could not distinguish between pre-existing mental health symptoms and conditions that emerged during the pandemic, complicating long-term mental health monitoring. This makes it challenging to interpret the findings regarding the true impact of COVID-19 on the participants' mental health.

The number of midwives who responded to the survey was relatively small, which may limit the generalizability of the results. In addition, the snowball sampling method used, along with the lack of personal contact, may have led to a non-representative sample, as some midwives may have felt too anxious to complete the questionnaire or may not have been interested in participating. The study was conducted specifically in Thessaly; hence, the findings cannot be generalized to other regions in Greece or internationally. Different regions may have experienced different levels of COVID-19 spread and implemented varying public health measures, which could have influenced the psychological impact on healthcare workers.

The studies referenced in the literature review showed heterogeneity, with variations in sample sizes, study periods, and locations, possibly impacting the comparability of the findings. Additionally, data collection was also difficult, particularly for midwives who do not use social media, limiting the reach of the survey and potentially excluding certain individuals from participation. Given these limitations, further research is needed to explore the long-term psychological effects of the pandemic on midwives and healthcare workers more extensively, especially in diverse settings and with larger, more representative samples.

5. Conclusion

The study's findings indicate that midwives in Thessaly experienced notable psychological distress due to their roles during the COVID-19 pandemic. Several factors were identified as contributing factors to poorer mental health and lower resilience: Midwives with poor or moderate

health conditions, individuals who spent less time with patients than before the pandemic, and individuals working in the public sector were found to have poorer mental health. In addition, individuals with high resilience reported fewer symptoms of depression and anxiety. Furthermore, midwives with greater clinical exposure during the pandemic experienced more stress compared to those in primary care settings.

The study also highlights the need for further research to explore the long-term psychological consequences of the pandemic. Future studies should focus on developing appropriate prevention, treatment, and recovery strategies for global public mental health in emergency situations like pandemics. The results of this study are significant and impactful, emphasizing the need for targeted psychological support and preventive interventions for midwives, particularly in the context of ongoing or future public health crises.

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Conflict of interest

The authors declare that they have no competing interest.

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Ethics approval and consent to participate

The approval for conducting the study was obtained from the Scientific Council of the Midwives Association of Thessaly. All participants provided written informed consent prior to their participation in the study.

Consent for publication

Participants consented to the publication of their anonymized data.

Availability of data

Data used in this work are available from the corresponding author upon reasonable request.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Validation and normalization of the youth risk-taking behavior assessment scale in an Iranian sample of substance abusers undergoing methadone maintenance treatment

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Abstract

Risk-taking (RT) behaviors play a key role in addiction and drug-related disorders. It is necessary to assess RT among young people, as they represent a key demographic vulnerable to drug and alcohol abuse. The aim of the present study was to validate and normalize the 18-item scale assessing youth RT behavior (RT-18) in a sample of substance abusers undergoing methadone maintenance treatment (MMT). In the present study, we employed a descriptive design and aimed to validate the RT-18 scale. The statistical population of the research included all substance-abusing (dependent) patients under MMT in Rasht, northern Iran. Using consecutive sampling, 220 patients were selected from three addiction treatment clinics and provided informed and voluntary consent to answer the RT-18 scale and the brief substance craving scale (BSCS). The test-retest reliability of the RT-18 scale was 0.74. Cronbach's alpha coefficient of RT-18, RT, and risk assessment (RA) subscales were 0.70, 0.88, and 0.55, respectively. Confirmatory factor analysis indicated that the modified two-factor structure for abusers under MMT provided a good model fit (β^2/degree of freedom = 2.74; weighted root mean square residual = 0.897; Tucker-Lewis index = 0.915; comparative fit index = 0.91; root mean square error of approximation = 0.061). The total RT-18 score was significantly correlated with BSCS scores (r = 0.26; p<0.01), but explained only a small proportion of variance ($F_{[1,218]}$ = 6.34; p=0.013). The results of the present study indicate that the Persian version of the RT-18 scale has acceptable reliability coefficients and may be used reliably in outpatient addiction treatment settings to assess RT behavior. However, the reliability coefficient of the RA subscale was low, and the total RT-18 score displayed limited predictive value for substance craving scores.

Keywords: Substance abuse; Risk-taking behavior; Validation; Normalization

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1. Introduction

Substance addiction is a behavior affected by various factors, such as curiosity, psychological processes, and peer pressure.[1] The latest edition of the diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR), identifies a significant feature of substance use disorder (SUD) as the presence of one or more

cognitive, behavioral, and physiological symptoms, which are characterized by frequent relapses, impaired control over consumption, and persistent drug-seeking behavior.[2] In addition to increasing the risk of physical and psychological disorders,[3,4] substance addiction imposes substantial harm on the affected individual, healthcare systems, and communities.[5] Research indicates that individuals with SUD experience deficits in cognitive functions, such as inhibitory control, impulsive behaviors, and risk-taking (RT) behavior.[6,7]

RT behavior involves exposing oneself to physical and psychological harm, or even death. RT not only includes engaging in risky behaviors but also refers to vulnerability and exposure to risks from the environment, peers, and incorrect or threatening personal beliefs and inclinations.[8,9]

Among the various treatment methods for individuals with substance addiction, methadone maintenance treatment (MMT) has received particular attention in Iran compared to other methods. MMT enables patients to refrain from using illegal substances. MMT can reduce substance use, mortality rates, and crime associated with substance use, and also improve patients' physical health and alleviate depression.[10,11]

In recent years, the prevalence of RT behaviors among adolescents and young adults in Iran has become a social issue, raising deep concerns at various managerial, academic, and public levels. The prevalence of substance use among young people is higher than in any other age group.[12] According to the 2023 report by the United Nations Office on Drugs and Crime, Iran has the highest ratio of opioid abusers to the population globally. The prevalence of SUD in Iran is approximately 5.4% of the adult population (individuals over 15 years old). This statistic indicates that Iran has one of the highest rates of substance use in the world. It is predicted that by 2030, the number of deaths and illnesses caused by tobacco use alone will reach 8 million annually.[13]

De Haan *et al.*[14] developed the young adult RT behavior-18 item (RT-18) assessment scale, which measures RT behavior as a dichotomous (yes/no) construct. This concise tool is significant due to its ability to assess RT behavior quickly with simple items. The RT-18 assessment scale consists of two subscales (RT and risk assessment [RA]), each with nine items. Higher scores on the RT subscale indicate greater involvement in RT, while higher scores on the RA subscale suggest a lower ability to perceive risks.

The RT-18 assessment scale has been applied across diverse populations and cultural contexts as a reliable tool for assessing RT tendencies. Originally validated among Dutch university students, social drinkers, and recreational drug users, it demonstrates strong internal consistency (Cronbach's α = 0.80–0.89) and a two-factor structure distinguishing RT behavior from RA.[14] The scale has been cross-culturally adapted into Portuguese and Spanish, with studies in Brazil and Argentina confirming acceptable psychometric properties. In Brazil, Rasch analysis supported the construct validity of a related measure, with minimal impact of age and sex on item functioning.[15] In Argentina, a Spanish version reported good reliability (ordinal α = 0.77) and concurrent validity among drivers, revealing that younger and daily drivers perceive lower risk.[16] The RT-18 assessment scale has been used in both non-clinical and high-risk populations, exhibiting sensitivity to group differences related to substance use and behavioral patterns. Evidence supports its utility in clinical, traffic safety, and research settings, particularly for young adults.

Despite the high prevalence of substance-related and behavioral addictions among youth,[17] there is a lack of culturally adapted, brief, and psychometrically validated tools to assess both RT and RA in this population. Existing measures are often lengthy or fail to capture both behavioral (RT) and cognitive (RA) dimensions. The RT-18 assessment scale—with its simple yes/no format, two subscales, and brevity—fills this gap. Validating the Persian version of the RT-18 assessment scale would provide clinicians and researchers with a practical and reliable tool for evaluating risk-related behaviors in methadone-maintained patients, supporting targeted interventions and longitudinal research.

Given that RT behavior plays a decisive role in predicting SUD[18] and can proactively identify at-risk individuals for policymakers and addiction treatment providers, it is essential to develop and standardize related psychological tools. Therefore, this study aims to validate a young adult RT behavior assessment tool, which can be completed in the shortest time and used for psychological evaluations.

2. Methods

2.1. Study design and participant characteristics

The research method is descriptive and involved the psychometric evaluation of tools. The statistical population consisted of all substance-addicted patients undergoing MMT in Rasht, northern Iran, in 2020. Inclusion criteria were as follows: (i) age range of 18 years or older, (ii) history of substance addiction according to DSM-5 (based on a semi-structured clinical interview), (iii) undergoing MMT for at least 30 days, (iv) being in the maintenance phase of treatment (*i.e.*, having achieved a stabilized dose of methadone), and (v) no concurrent substance abuse

(based on urine tests). Exclusion criteria were the presence of withdrawal symptoms or substance abuse (indicating instability of the patient) and concurrent substance abuse (other than nicotine dependence).

2.2. Sampling procedure and data collection

All authorized public and private centers under the supervision of the Gilan University of Medical Sciences and Welfare Organization in Rasht were initially listed. Three centers (Mehr Addiction Treatment Clinic, "Rah-e Sabz" Addiction Treatment Clinic, and Behavioral Disorders Center [ChomarSara-Rasht]) were then randomly selected from this list. After obtaining informed consent from the patients, all individuals with records who met the criteria were interviewed by a trained psychologist (with a master's degree in psychology) for SUDs to confirm the presence of addiction disorders and related conditions (especially opioids, according to DSM-5). Finally, participants responded to the questions while waiting in the office room under the supervision of the examiner.

This study was conducted in two phases: (i) a preliminary study and (ii) a main study. Since no validated and standardized Persian version of the RT-18 assessment scale was available, a rigorous translation and adaptation process was undertaken. First, the original English version of the RT-18 assessment scale was independently translated into Persian by two psychologists with expertise in psychometric assessments. Subsequently, the Persian version was back-translated into English by a senior expert in translation studies. The principal investigator (corresponding author) then reviewed all three translations (the original, forward-translated, and back-translated versions), resolved discrepancies, and finalized the Persian adaptation of the RT-18 assessment scale in a joint session. The translated scale was then piloted on a sample of 30 individuals with SUDs to assess clarity and cultural appropriateness. This multi-step approach—combining forward translation, expert consensus, back-translation, and pilot testing—ensured linguistic accuracy and maintained the original scale's psychometric properties.[19]

The RT-18 assessment scale is a tool designed to assess risk-related behaviors in youth through two subscales: (i) RT, which reflects engagement in potentially harmful behaviors, and (ii) RA, which measures cognitive evaluation of risks. The scale primarily assesses trait-like characteristics rather than transient states, aligning with theories of impulsivity and sensation-seeking[20] and cognitive decision-making.[21] Although situational factors may introduce some state-like variability, the RT-18 assessment scale is interpreted as a measure of stable individual differences. Its dual foundation in personality and behavioral economics[22] enhances its utility in studying youth risk behavior.

In the preliminary study phase, 30 substance abusers undergoing MMT were tested using the RT-18 assessment scale through a convenience sampling method. To determine the test-retest reliability, the same individuals were retested after 3 weeks. The formula for estimating trait means in the population was used to determine the sample size in the main study.[23] The final sample size needed for normative data was calculated by inputting the standard deviation obtained from the initial RT-18 assessment (3.09). In the sample size formula, a confidence level of 95% (z = 1.96) and a tolerable error (d^2) of 0.05 were considered for increased accuracy.

Due to the limited number of active treatment cases in the studied treatment centers (approximately 260 patients), a corrected sample size formula was used to calculate the mean of a trait in a finite population.[24] The corrected sample size based on the finite population was estimated to be 192. To account for outliers and missing values, an additional 15% dropout rate was added, bringing the corrected sample size to 220 for the treatment centers. This number was selected using a non-probabilistic consecutive sampling method.

2.3. Ethical considerations

Before the study commenced, the purpose of the research was explained to all patients in general terms, and their informed consent was obtained. They were assured that their personal information would remain confidential with the researcher.

2.4. Research tools

2.4.1. Risk-taking behavior assessment scale (RT-18)

This tool assesses RT behavior and was developed by de Haan *et al.*[14] The RT-18 scale consists of 18 dichotomous (yes/no) items. The RT-18 scale has two subscales, each with nine items: (i) RT (*e.g.*, "I sometimes like to do things that are a little frightening"), which has a Cronbach's alpha of 0.80, and (ii) RA (*e.g.*, "Do you mostly speak before thinking things out?"), with a Cronbach's alpha of 0.57. Higher scores on the RT subscale indicate greater engagement in RT behavior, while higher scores on the RA subscale suggest lower risk perception ability. In de Haan *et al.*'s study,[14] the internal consistency reliability and test-retest reliability of this tool were reported as 0.886 and 0.94, respectively. The concurrent validity of RT-18 was confirmed through high correlations with the Cambridge Gambling Task. The Persian version of this tool was initially prepared through translation and back-translation processes. It was then piloted with a sample of 30 MMT

patients to determine test-retest reliability, with the same individuals retested after 3 weeks (during a follow-up visit). The Pearson correlation coefficient for this test-retest was 0.74 (95% confidence interval: −6.80–−4.66; degree of freedom [df] = 29, $p<0.0001$). In this study, the Cronbach's alpha was 0.70 for all items of the tool. The Cronbach's alpha coefficients (equivalent to the Kuder-Richardson formula-20 [KR20] for this type of scale) were 0.88 and 0.55 for the RT and RA components, respectively.

2.4.2. Brief substance craving scale (BSCS)

In this study, the BSCS was used to measure craving for relapse. Relapse was defined as patients who were previously diagnosed with substance dependence, now exhibiting a craving for relapse during their MMT period. This scale is an eight-item self-report tool developed by Somoza *et al.*[25] that measures the duration, frequency, and intensity of substance craving on a five-point Likert scale from never (0) to very high (4). This scale was completed through an interview conducted by a trained psychologist with the MMT patient. The test demonstrated acceptable concurrent validity with strong correlations to addiction severity scales. The internal consistency reliability of the BSCS, as measured by Cronbach's alpha, was reported to be 0.88. In Iran, Basharpoor *et al.*[26] reported its internal consistency reliability as 0.78. In this study, after removing items one and five, which inquire about dependence on a specific substance, Cronbach's alpha for the remaining six items was 0.85.

2.5. Data analysis

To determine the test-retest reliability in this study, Pearson correlation coefficients of RT-18 scores were calculated between different administration times, involving at least 30 patients. To this end, 30 patients who initially completed the RT-18 assessment were re-assessed with the same tool during their follow-up visit after 3 weeks. The scores from these two assessment points were then correlated. In addition, a paired Student's *t*-test was used to determine the differences between the two measurements of RT-18. Furthermore, Cronbach's alpha was used to evaluate the internal consistency reliability of the research tools. Item-total correlations for each of the subscales of RT behavior and RA were also used for construct validity analysis. For assessing the reliability of individual RT-18 items, Cronbach's alpha was computed separately after the exclusion of each item. Concurrent validity was evaluated by examining the relationship between scores on the Persian version of RT-18 and scores from established measures that were expected to have significant correlations based on prior research (BSCS).

Given that the underlying factors of the RT-18 scale were previously identified,[14] this study focused solely on the confirmatory factor analysis (CFA) of the RT-18 scale using maximum likelihood estimation in Mplus 7.4 software (Muthén & Muthén, USA).[27] Indices, such as Chi-square (χ^2), ratio of Chi-square to degrees of freedom (χ^2/df), Root Mean Square Error of Approximation (RMSEA), goodness-of-fit index (GFI), Bentler-Bonett normed fit index, Tucker-Lewis index (TLI), and comparative fit index (CFI), were evaluated to assess the goodness of fit of the two-factor model of the RT-18.[28] Moreover, the convergent and divergent construct validity of the RT-18 was assessed using the Fornell and Larcker approach,[29] which involved evaluating the average variance extracted (AVE), maximum shared squared variance (MSV), and average shared squared variance (ASV). To establish convergent validity, AVE values should be >0.5, and composite reliability (CR) > 0.7 and CR > AVE. For divergent validity, MSV and ASV should be less than AVE.[30] Finally, using raw scores, means, and standard deviations for the total score and subscales of RT-18, a test norm table was prepared, including percentile ranks and standardized scores (*z* and *T* scores). All analyses were performed using the Statistical Package for the Social Sciences-24 (IBM Corporation, USA).

3. Results

The data were obtained from 248 patients, but due to defects in completing some questionnaires, the data of only 220 patients were prepared for psychometric analysis. This study presented descriptive statistics (mean and standard deviation) related to RT behavior and substance craving. The substance-craving variable had a mean of 2.77 and a standard deviation of 3.50. The RT behavior variable had a mean of 3.40 and a standard deviation of 8.39. Regarding the duration of substance use, 56.5% had used substances for <10 years, 30.6% between 10 and 20 years, 10.1% for between 20 and 30 years, and 2.8% for more than 30 years. Approximately 51.6% of respondents reported a history of substance withdrawal, and among the 128 individuals with a history of withdrawal, 71.1% had only one past instance of substance withdrawal. Table 1 reports other demographic characteristics of the respondents.

Table 2 displays the results of descriptive statistics, item-total correlations, and reliability analysis for the RT-18. As displayed in this table, all item-total correlation values, except for items 1, 3, 11, and 12, were moderate to strong ($p<0.0001$), indicating the internal consistency of the RT-18. Cronbach's alpha coefficients, after item removal, ranged from 0.65 to 0.76. One reason the corrected item-total correlations are weak for items 1, 3, 11, and 12 is that their correlations were calculated with the total RT-18 score, while these items belong to the "risk assessment" subscale. Therefore, these items were not removed from the Persian version of the RT-18.

Table 1. Demographic characteristics of substance-addicted patients undergoing methadone maintenance treatment (MMT) (*n*=248)

Characteristics	*n*	%
Gender		
Female	22	8.9
Male	226	91.1
Age (years)		
≤30	55	22.2
31–40	135	45.2
41–50	56	22.6
Education level (years)		
<5	64	25.8
5–10	84	33.9
>10	100	40.3
Marital status		
Single	44	17.7
Married	185	74.6
Divorced	14	5.6
Widowed	5	2

Table 2. Mean, standard deviation, and item-total correlation results and reliability analysis for young adult risk-taking behavior-18 items (*n*=220)

Item	Mean	Standard deviation	Corrected item-total correlation	Cronbach's alpha if item deleted
r1	0.7696	0.42207	0.216	0.689
r2	0.6728	0.47027	−0.402	0.747
r3	0.3318	0.47195	0.276	0.683
r4	0.4009	0.49122	0.692	0.636
r5	0.3963	0.49026	0.590	0.648
r6	0.4562	0.49923	0.588	0.648
r7	0.3917	0.48926	0.639	0.642
r8	0.2627	0.44110	0.319	0.679
r9	0.5023	0.50115	−0.521	0.762
r10	0.6682	0.47195	−0.563	0.761
r11	0.4240	0.49533	0.060	0.706
r12	0.3502	0.47814	0.184	0.693
r13	0.3410	0.47515	0.429	0.667
r14	0.3871	0.48821	0.746	0.630
r15	0.6221	0.48598	0.515	0.657
r16	0.5300	0.50026	0.531	0.654
r17	0.3548	0.47957	0.630	0.644
r18	0.4747	0.50051	0.447	0.664

Table 3 presents the Pearson correlation coefficients between RT behavior and substance craving. The correlation matrix indicates a positive and significant relationship between substance craving and RT behavior (p<0.01). As expected, the correlation coefficients between RT behavior scores and craving for relapse on BSCS were significant at the 0.01 level, thereby confirming the construct validity of the RT-18 scale. In addition, the positive correlations displayed in Table 3 suggest that higher overall RT behavior scores are associated with greater substance craving in MMT patients (p<0.01), confirming the concurrent validity of the RT-18 scale.

Table 4 assesses construct validity using CFA (n = 220). In the modified first-order CFA, the Chi-square GFI was χ^2 = 324.059 (p<0.001). Other fit indices were evaluated to assess model fit: RMSEA = 0.061; TLI = 0.915; weighted root mean square residual = 0.897; and CFI = 0.956; all confirming a good fit of the final model (Table 4 and Figure 1). The correlation coefficient between the two factors in Mplus 7.4 was 0.243, indicating that the overlap between the two factors was 5.9%; hence, they can be considered distinct factors.[27]

The results of the first-order CFA (Table 5) indicate that the AVE and CR values for both factors were >0.5 and 0.7, respectively; AVE values for each factor were greater than

Table 3. Pearson correlation matrix between risk-taking behavior and substance craving (*n*=220)

Variables	I	II	III	IV
I	1			
II	0.17*	1		
III	0.04	0.24**	1	
IV	0.26**	0.94**	0.40**	1

Notes: I refers to "substance craving;" II refers to "risk-taking (RT, first subscale of the test);" III refers to "risk assessment (RA, second subscale of the test);" and IV refers to "risk-taking behavior" (total score). *p<0.05, **p<0.01.

Table 4. Fit indices in confirmatory factor analysis of young adult risk-taking behavior-18 items (*n*=220)

Model	χ^2	df	*p*	CMIN/df	RMSEA	TLI	WRMR	CFI
Primary	384.858	134	<0.001	2.872	0.068	0.904	0.901	0.938
Secondary	324.059	131	<0.001	2.473	0.061	0.915	0.897	0.956

Note: Fit indices: CFI, TLI (>0.9); RMSEA (<0.08); WRMR (<1); CMIN/DF (<3 good; <5 acceptable).
Abbreviations: CFI: Comparative fit index; CMIN/DF: Chi-square/degree-of-freedom ratio; RMSEA: Root mean square error of approximation; TLI: Tucker Lewis index; WRMR: Weighted root mean square residual.

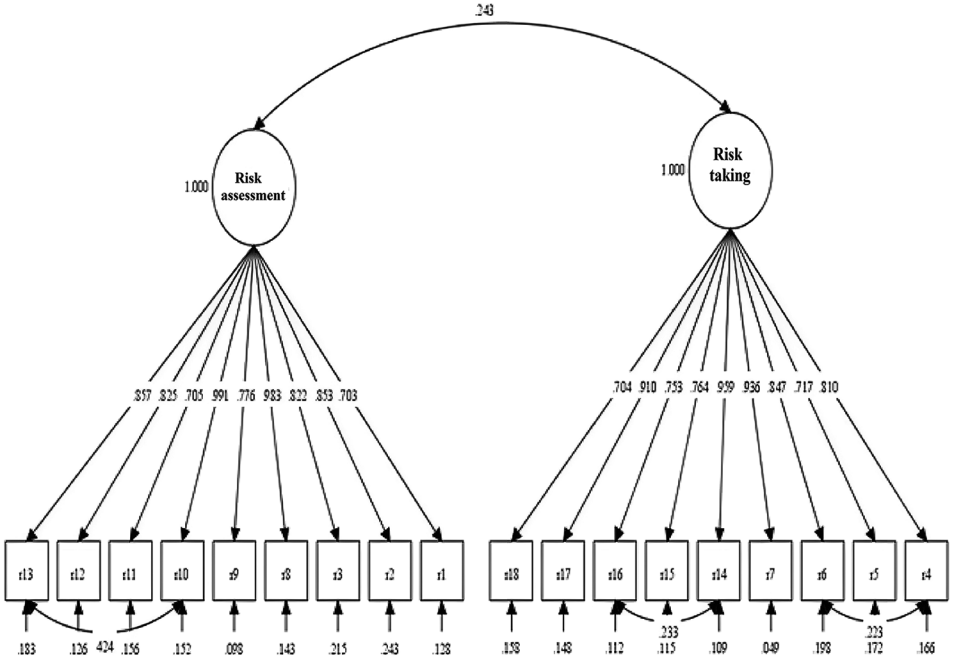

Figure 1. Risk-taking behavior-18 item structure: Modified model from first-order confirmatory factor analysis

Table 5. Convergent and divergent validity indices for the young adult RT behavior-18 items scale (*n*=220)

Factor	CR	ASV	MSV	AVE	Correlation	Shared variance (%)
RT	0.951	0.374	0.059	0.689	0.243	5.9
Risk assessment	0.955	0.322	0.059	0.706		

Abbreviations: ASV: Average shared squared variance; AVE: Average variance extracted; CR: Composite reliability; MSV: Maximum shared squared variance; RT: Risk-taking behavior scale.

CR; and the AVE values for each factor were greater than both ASV and MSV. Therefore, the results indicate that the RT-18 construct has adequate convergent and divergent validity.

Although items 1, 3, 11, and 12 had weak corrected item-total correlations with the total RT-18 score (Table 2), these items demonstrated strong factor loadings (0.703, 0.822, 0.705, and 0.825, respectively) according to Figure 1 in relation to their associated latent variable (*i.e.*, RA) in the first-order CFA. These results support the decision to retain these items in the Persian version of RT-18.

A bivariate regression analysis was conducted to assess predictive criterion validity and determine how much of the variance in craving for relapse (as the criterion variable) could be explained by the total score of RT-18 (as the predictor variable) (n = 220). The results indicated that RT behavior (total RT-18 score) significantly explained only 3% (R^2 = 0.028) of the variance in craving for relapse scores ($F_{[1,218]}$ = 6.34; p=0.013). Considering the standardized regression coefficients (β), it can be inferred that individuals with higher RT behavior report greater craving for relapse (β = 0.17; p=0.013). Thereafter, a norm table was prepared based on converting raw scores to standardized scores (z and T scores) and calculating percentile ranks (Table 6). According to the results in Table 6 and the raw scores of each participant, it is possible to determine what percentage of individuals have higher RT behavior compared to the participants. For example, a standardized z-score of 0.479 for a person scoring 10 on RT-18 indicates that their level of RT is higher than 67% of substance users.

4. Discussion

The present study aimed to validate, assess the reliability, and establish norms for the RT-18 scale for Iranian youth in a sample of substance users undergoing MMT. The findings from Pearson correlation coefficients indicated that all items, except for items 1, 3, 11, and 12, were moderately to strongly related to the total test score. This result reflects the internal consistency of the RT-18 scale.

In this study, Cronbach's alpha for the Persian version of RT-18 was found to be 0.70. The Cronbach's alpha coefficients for the components of RT behavior and RA were 0.88 and 0.55, respectively. These findings are consistent with the overall RT-18 score in the study by de Haan *et al.*,[14]

Table 6. Conversion of raw RT scores and subscales (RTB and RA) to standardized scores for percentile ranks of the entire sample (*n*=220)

Normative data of RT total score				Normative data of the RTB subscale				Normative data of the RA subscale			
PR	**RS**	***z***	***T***	**PR**	**RS**	***z***	***T***	**PR**	**RS**	***z***	***T***
<5	3	−1.54	34	<16	0	−1.25	37	<1	1	−2.88	21
13	4	−1.25	37	31	1	−0.942	40	5	2	−2.02	29
30	5	−0.965	40	44	2	−0.628	43	25	3	−1.15	38
39	6	−0.676	43	54	3	−0.314	46	54	4	−0.294	47
45	7	−0.387	46	57	4	0	50	84	5	0.569	55
56	8	−0.098	49	63	5	0.314	53	99	6	1.433	64
64	9	0.19	51	70	6	0.628	56	>99	7	2.297	72
67	10	0.479	54	80	7	0.942	59	-	-	-	-
77	11	0.768	57	89	8	1.256	62	-	-	-	-
86	12	1.05	60	>99	9	1.517	65	-	-	-	-
90	13	1.346	63	-	-	-	-	-	-	-	-
98	14	1.635	66	-	-	-	-	-	-	-	-
>99	15	1.923	69	-	-	-	-	-	-	-	-

Abbreviations: PR: Percentile ranks; RA: Risk assessment subscale; RS: Raw scores; RT: Risk-taking behavior scale (total); RTB: Risk-taking behavior subscale.

where Cronbach's alpha for RT-18 in a student population and a general population of Dutch youth were reported as 0.886 and 0.80, respectively. These results indicate that the reliability of the RT behavior component and the unified form of the RT-18 tool is at least at an acceptable level,[31] and each measures a similar concept and structure. However, internal consistency was weak for the RA component. Consistent with the present study, Stamates and Lau-Barraco[32] found that only the RT subscale could predict alcohol use, while RA was not associated with any alcohol use outcome. This finding likely reflects the inverse and cautious nature of the RA questions, which explore the positive aspect of RT behavior and may not be well-aligned with the RT component.

Cross-culturally, RT is consistently higher in men and drug users, as seen in both Dutch and Iranian samples. However, in the Iranian MMT sample, RA demonstrated poor reliability and weak association with craving, suggesting a cultural or clinical divergence where risk behavior may be more habitual and less cognitively regulated compared to the general Dutch youth population.

In addition, in a pilot study involving 30 individuals undergoing MMT, the test-retest reliability coefficient after 3 weeks was 0.74. In the main study by de Haan *et al*.,[14] the test-retest reliability with a 2–4 week interval was reported as 0.94. Although test-retest reliabilities in both the Iranian and Dutch studies are considerable, the primary differences in these coefficients are likely understandable due to the differences between the Iranian substance user sample and the Dutch students.

The CFA results indicated that the best-fitting model for MMT patients included two modified factors: RT and RA. This is consistent with de Haan *et al*.'s[14] study, which also emphasized the two-factor structure of the tool through CFA. CFA indicated that freeing the covariance terms between the errors of items 13 and 10 in the RA component, as well as between the errors of items 16 and 14 and items 6 and 4 in the RT component, would confirm the fit of this two-factor model in the Iranian substance user population. This contrasts with the study by Stamates and Lau-Barraco,[32] where RA was not associated with alcohol use, and only the RT factor predicted alcohol use and its consequences.

Regarding concurrent and predictive criterion validity, the findings of this study revealed that the total RT-18 scores have a weak relationship with the substance craving scale (r = 0.26; p<0.01) but explain a significantly small amount of its variance (only 3%; F = 6.34; p=0.013). Previous studies, including de Haan *et al*.'s,[14] also indicated a significant correlation between RT-18 scores and scores on the Cambridge Gambling Task, with recreational substance users scoring significantly higher on RT-18 compared to those consuming alcohol. In addition, Soni *et al*.[12] found a significant correlation between RT-18 scores and impulsive behaviors. These results partially align with the present study and marginally support the concurrent and predictive validity of the RT-18 tool.

These findings can be interpreted from two perspectives. First, the RT-18 scale is relatively reliably

correlated with external criteria that have previously been validated in the Iranian population. Second, it suggests that interventions aimed at reducing RT behavior, improving behavioral control, and enhancing precautionary behaviors could play a significant role in reducing substance cravings. This study found that only a negligible proportion of variance in relapse propensity was explained by RT-18 total scores. One explanation for this finding relates to the multidimensional and complex nature of substance craving.[33] In other words, RT behavior represents just one psychological dimension of craving and cannot alone account for its extensive variability. Even if RT behavior correlates with craving, this association may be mediated or moderated by other factors, such as dopaminergic activity, stress levels, or drug availability,[34] thereby diminishing its independent predictive power. Furthermore, prior research indicates that some individuals with high RT propensity may experience reduced craving due to stronger self-control or better social support.[35] Such individual differences further attenuate the explanatory contribution of RT behavior. Biological factors also play a significant role; for instance, dysregulation of the dopaminergic system and reduced D2 receptor density in addicted individuals are known to intensify craving.[36]

These findings suggest an important hypothesis for future investigation: incorporating a battery of biological, psychological, and social measures could yield a more accurate prediction of substance craving. An alternative interpretation of the minimal variance explained relates to our study's sample characteristics. Participants were all undergoing MMT, meaning they had consistent access to pharmacological craving suppressants. This likely constrained the observable variance in relapse propensity that could be attributed to RT-18 scores.

RT and RA represent distinct yet interrelated constructs in behavioral decision-making. RT reflects a propensity toward engaging in potentially harmful behaviors, often associated with impulsivity and reward sensitivity.[20] In contrast, RA involves the cognitive appraisal of potential risks and benefits, relying on intact executive functions and prefrontal regulation.[21] Although these dimensions typically show moderate intercorrelation in the general population, the present study found a notably weak correlation (r = 0.24) among individuals undergoing MMT, suggesting a functional dissociation in this clinical group. This attenuated relationship may stem from several interrelated factors. Chronic opioid use is associated with structural and functional impairments in prefrontal brain regions critical for risk evaluation,[37] potentially decoupling behavioral choices from rational deliberation. In addition, prolonged substance use may lead to desensitization to negative consequences, weakening the influence of cognitive risk appraisal on behavior.[38] While methadone stabilizes cravings, it may not fully reverse underlying decision-making deficits, allowing impulsive or habitual RT to persist despite partial cognitive recovery. Furthermore, in the context of addiction, behaviors such as drug use may be motivated more by immediate relief from withdrawal than by a deliberate cost-benefit analysis.

Furthermore, percentile norms for the total scores and each subcomponent of RT-18 have been prepared and made available in a norm table. The key feature of norm tables is that they allow experts and counselors to compare an individual's scores with a reference group—considered representative of the population—using percentile ranks. However, it should be noted that the sample of this study was predominantly young and consisted of substance users undergoing MMT, thus limiting the generalizability of the results to other populations. The introduced tool for assessing RT behavior, aimed at evaluating the potential and likelihood of risky behaviors among substance users as a trait, may not be suitable. This is because the intensity of risky behaviors is a function of various factors, such as duration of abstinence, dosage of addiction treatment medications, being under treatment, or the lack of psychological interventions, among others. In addition, using this tool and its norms to assess RT in situations where the substance user has not yet committed to their treatment is not recommended.

The present study had several limitations. The findings are limited to individuals over 18 years old who were undergoing MMT. In addition, the samples were consecutively selected from treatment units, indicating a non-random sampling method. Based on these limitations, future research should consider developing this tool or other appropriate tools for adolescent populations who are at risk for RT behaviors, especially regarding substance use and unprotected sexual relationships. Future studies are also recommended to compare substance users with normative groups and to determine the cutoff points of this tool for screening at-risk individuals. It is also recommended that, due to potential cultural and linguistic effects on the structure of RT-18, future studies employ exploratory factor analysis to re-examine the underlying factors of RT-18 in the Iranian population. Furthermore, the observed negative or low item-total correlations for several items in the RA subscale suggest potential issues with the internal structure of the scale, which should be further examined in future studies. To enhance convergent validity and improve the accurate prediction of substance craving, it is recommended to employ multifactorial models that incorporate a combination of biological, psychological, and social variables. For instance, behavioral tasks

(*e.g.*, delay discounting, go/no-go paradigms) or biological indicators could be utilized to triangulate risk-related constructs beyond self-report measures. In addition, age, gender, cultural background, education level, and even distinct substance use patterns may significantly influence RT behavior scores. Therefore, we recommend that future research employ subgroup analyses to examine the role of these factors. Where appropriate, separate norm tables should be developed for different subgroups to enhance measurement precision. To minimize the effects of memory and response recall for a more accurate assessment of test-retest reliability, it is recommended to increase the time interval for administering the RT-18 scale.

5. Conclusion

The Persian version of the RT-18 scale demonstrated acceptable reliability and construct validity for assessing RT behavior in Iranian patients undergoing MMT, with the two-factor model exhibiting adequate fit when covariance terms were released. The RT-18 scale yielded consistent results and may be useful in outpatient addiction settings for evaluating RT tendencies. However, the RA subscale presented low internal consistency, and the total RT-18 score accounted for only a small proportion of variance in substance craving, indicating limited predictive utility. These findings suggest that while the RT-18 scale is a practical tool for measuring RT in this population, caution is warranted in interpreting the RA dimension and its clinical implications.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

All study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki (2013). All participants provided informed consent, confirming their satisfaction with participating in this research.

Consent for publication

The participants gave informed consent to publish their data in this study.

Availability of data

The data that support the findings of this study are available on request from the corresponding author.

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Journal of Clinical and Basic Psychosomatics

CASE REPORT

Addressing evaluation challenges and incorporating psychotherapeutic interventions in the diagnosis of functional seizures: A case report

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Abstract

Functional seizures (FSs) are a subset of functional neurological disorders frequently misdiagnosed due to their clinical overlap with neurological conditions. Unlike epileptic seizures, they occur without abnormal neuronal discharges and manifest through diverse motor, sensory, and cognitive symptoms. This case report presents the diagnostic trajectory of a patient initially misdiagnosed with stroke-related motor symptoms and later epilepsy, subsequently reevaluated at Ramos Mejía Hospital in Buenos Aires. A comprehensive multidisciplinary assessment involving a differential diagnosis process was conducted to confirm the diagnosis of FSs by ruling out epilepsy, autoimmune encephalitis, and concomitant psychosis. The implementation of targeted psychoeducation, symptom monitoring, and interventions based on the integrative cognitive model resulted in significant clinical improvement, including reduced seizure frequency and enhanced functional mobility. Furthermore, psychotherapeutic strategies facilitated patient acceptance of the diagnosis and adherence to treatment. This case underscores the diagnostic challenges associated with FSs and highlights the importance of a multidisciplinary, individualized approach to optimize symptom management and patient outcomes.

Keywords: Functional neurological disorders; Functional seizures; Misdiagnosis; Psychotherapeutic intervention; Diagnostic challenges

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1. Introduction

Functional neurological disorders (FND) are syndromes caused by neural network dysfunction rather than structural brain anomalies, including motor symptoms, functional seizures (FS), chronic functional dizziness, cognitive dysfunction, functional

somatosensory or visual symptoms, and functional speech symptoms.[1,2] FS mimic epileptic seizures without abnormal brain discharges, presenting with various motor, sensory, or cognitive symptoms.[3,4] Diagnosis is based on clinical signs differentiating FND from other conditions.[5,6] FNDs are the second most frequent reason for consultation in outpatient neurological centers all over the world.[7] Studies suggest a prevalence of FNDs in the range of 50 – 100 cases/100,000 people.[8]

This article details an FS case initially misdiagnosed as stroke, epilepsy, or autoimmune encephalitis. A psychotherapeutic program combining psychoeducation, cognitive behavioral therapy, mindfulness, and interpersonal therapy improved patient understanding, acceptance, and treatment adherence. The diagnostic steps and therapeutic outcomes of this case are illustrated in the paper.

2. Case presentation

2.1. Patient's information

A 52-year-old woman was admitted to Ramos Mejía Hospital (RMH) in January 2022, displaying incoherent speech, temporal and spatial disorientation, hallucinations, manual automatisms, and altered consciousness.

2.2. Previous medical history and treatment

The patient has a history of an accident in 2018 leading to motor disabilities, right hemiparesis, and language impairment. Subsequent ischemic strokes were reported in 2019 and 2020. In March 2020, she presented behavioral alterations, cognitive and language impairments, memory loss, and epileptic seizures, and was managed with lacosamide 100 mg every 12 h, valproic acid 250 mg every 12 h, and quetiapine 125 mg/day in the morning and 25 mg/day at night. Despite treatment, symptoms persisted, and a 2021 hospitalization led to the identification of her condition as status epilepticus, reinforcing the epilepsy diagnosis.

2.3. Clinical findings

The patient presented with incoherent speech, disorientation, automatisms, and altered consciousness. Two types of episodes were reported: brief episodes (2 – 3 min) with crying, tremors, and disorientation (type 1); and longer episodes (20 – 30 min) with oromandibular movements, hyperventilation, self-injury, and memory gaps (type 2). Both could manifest during wakefulness or sleep. With regard to these episodes, the patient described a lack of warning before their onset, post-episode confusion, and self-injury episodes marked by a gap in memory, followed by a period of drowsiness. Her family suspected that she experienced visual hallucinations during these episodes. Additional symptoms included sleep disturbances, a history of depression, sleepwalking episodes, and headaches. Her motor difficulties required her to use a wheelchair for mobility. Diagnostic studies were initiated during hospitalization.

2.4. Diagnostic assessments/studies

Medical reports from a previous brain magnetic resonance imaging (MRI) described small chronic ischemic lesions, initially interpreted as evidence of a stroke in 2018, with hemiparetic sequelae. However, since this MRI was conducted at another hospital, the exact location and characteristics of the lesions remain unknown. Moreover, the patient's clinical presentation did not fully align with this diagnosis. A follow-up MRI (including diffusion and apparent diffusion coefficient mapping) (Figure 1) and computed tomography scan were normal. Neurologic examination, as part of the physical assessment, was normal and not congruent with the stroke history. These studies, along with the patient's clinical presentation, were collectively evaluated by professionals specializing in abnormal movements, epileptologists, and vascular specialists.

A 2-h electroencephalogram (EEG) was conducted due to suspected epileptic type 1 episodes, but no epileptiform activity was detected. Type 2 episodes suggested encephalitis, so autoimmune serum and cerebrospinal fluid analyses were conducted, yielding negative results. This panel utilized a fixed transfected cell method with indirect immunofluorescence as the detection technique. The tested antibodies and their cut-off values were: NMDA receptor, cut-off 1:10; contactin-associated protein 2, cut-off 1:10; AMPA receptor, cut-off 1:10; leucine-rich glioma-inactivated protein 1, cut-off 1:10; dipeptidyl aminopeptidase-like protein 6, cut-off 1:10; GABA B receptor, using monkey cerebellum as substrate, cut-off 1:50; tested antibodies were A-NMO-IgG, A-Hu (ANNA-1), A-Ri (ANNA-2), and A-Yo (PCA-1). Empirical immunotherapy was not considered due to the three-month wait time for results. A video-EEG was conducted, through which four events were observed without EEG correlation (Figure 2).

An informed consent was obtained, and a pseudonym was used for privacy. The case study was approved by RMH's ethics committee.

2.5. Presumptive diagnosis and treatment plan

The tests ruled out stroke, autoimmune encephalitis, and epilepsy, and, due to the patient's progression, chronic psychosis was also excluded. A diagnosis of FS was made based on clinical events and video-EEG results. The patient was referred to the mental health team, antiepileptic medication was gradually discontinued, and

lorazepam (3 mg/day) was added for insomnia. Quetiapine (125 mg/day) was continued for anxiety and insomnia.

2.6. Mental health intervention (Mental Health Team of the RMH Epilepsy Center)

After the diagnosis, the patient was referred to the mental health team at the RMH Epilepsy Center's – consisting of a psychiatrist and two psychologists specializing in FS – for monthly psychoeducational interviews (60 – 90 min each).

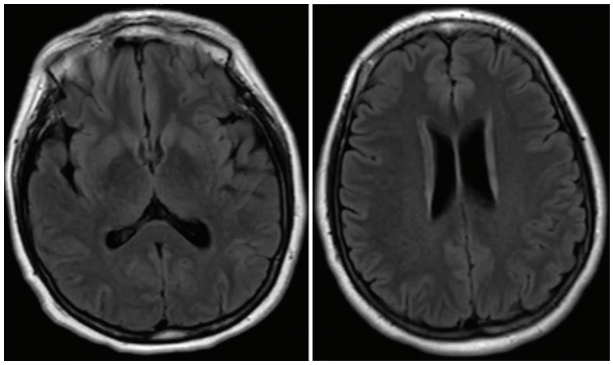

Figure 1. Magnetic resonance imaging findings. No abnormalities were observed in the evaluated anatomical structures. No signal abnormalities were observed in the diffusion. There is no evidence of chronic ischemic injury.

These sessions aimed to familiarize the patient and her family with the FS diagnosis and prepare her for psychotherapeutic treatment.

The initial session focused on differentiating FS from epilepsy, particularly in terms of etiology and EEG findings. The patient remained disengaged throughout the discussion.

Subsequent sessions focused on psychoeducation, with an emphasis on exploring the FS diagnosis and addressing symptom management. Grounding techniques were introduced to assist in managing seizures and motor symptoms, significantly enhancing the patient's ability to control her condition. As the sessions progressed, a notable improvement in seizure control and symptom moderation was observed. Family involvement in the psychoeducation process was encouraged.

An Excel spreadsheet for seizure tracking was implemented initially for recording occurrences and eventually for identifying triggers and behaviors post-seizures, although the family's consistency in maintaining these records varied.

By the fourth session, improved attention allowed for deeper psychoeducation using Brown and Reuber's

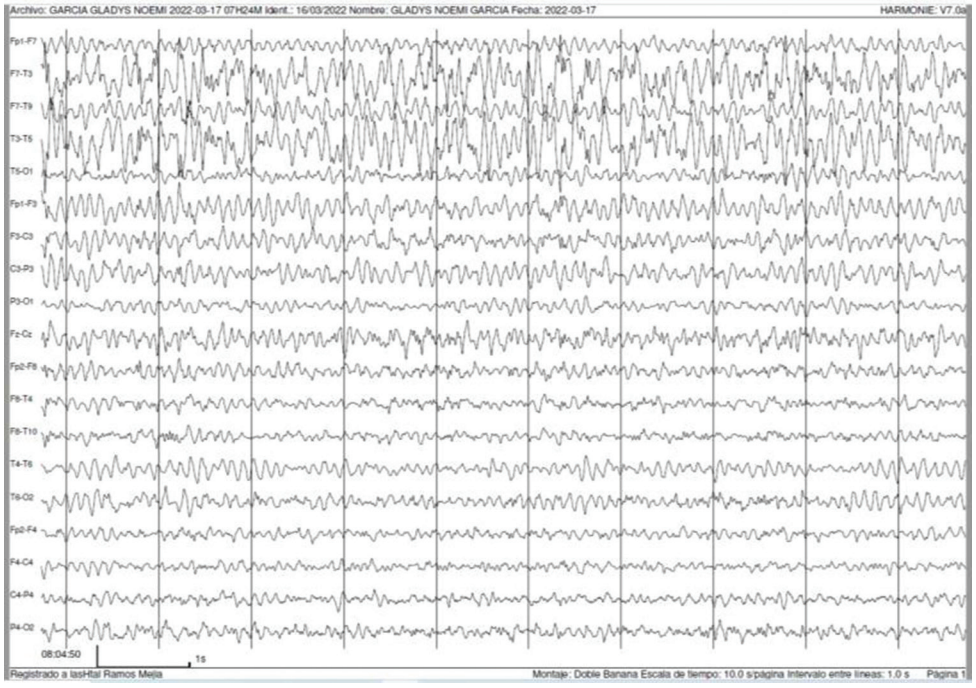

Figure 2. Video-electroencephalographic (EEG) finding. The tracing during the study showed movement artifacts without evidence of epileptiform activity. The patient presented four clinical events, characterized by abrupt onset of searching movements of the head to the sides, prima facie evidence of disorientation, and dystonic facial posture. Automatic gripping movements in both hands were observed. The patient did not respond to interrogation and continued with automatisms while issuing a phrase such as "where is the son?" The episodes extended in variable time from 15 min to 3 h. At the end of the events, the patient fell asleep.

integrative cognitive model (ICM),[9] which highlights the brain's predictive role in perception and emotion. The model proposes that FS arises from the automatic activation of erroneous procedural representations (schemas), distorting perception and action. This disruption affects the integration of behavior, memory, identity, consciousness, and motor control.

Later sessions addressed family dynamics, encouraging the patient to engage actively, recognize prodromal seizure symptoms, and apply control techniques, such as mindfulness and breathing exercises.

Gradual mobility improvements became evident by the fifth session, and by the seventh, the patient had shifted to using a walking stick, demonstrating increased daily autonomy. Her growing interest in attending a day center prompted further tailored psychoeducation. In addition, during the seventh meeting, she exhibited enhanced alertness, fluency, and proactive engagement in family activities, and she began inquiring about her diagnosis and the rationale behind previous exclusions of other possible conditions or diagnoses.

Physiotherapy and psychological treatment were recommended. The series of interventions and psychoeducation enhanced the patient's understanding of her condition, fostering increased self-care, a proactive attitude, and progress toward acceptance and self-management.

3. Discussion

Diagnosing conditions, such as epilepsy, psychosis, FND, FS, stroke, and autoimmune encephalitis can be challenging due to overlapping symptoms and the absence of definitive tests. Healthcare professionals must conduct thorough evaluations for accurate diagnoses and appropriate treatment.

In this case report, we provide a comprehensive account of the medical history of a 52-year-old woman at RMH. Throughout the diagnostic process, various potential diagnoses were explored and excluded. Ultimately, the process culminated in the confirmation of FS as the underlying condition.

In this specific case of stroke, epilepsy, and autoimmune encephalitis with suspicion of concomitant psychosis were considered but subsequently ruled out based on diagnostic tests, the clinical presentation of symptoms and the case evolution.

Autoimmune epilepsy, an autoimmune disorder, involves immune-mediated neuroinflammation leading to diverse neurological symptoms, including psychiatric disorders, cognitive dysfunction, and seizures.[10] Psychosis, present in approximately 7% of epilepsy cases,[11] poses a challenge for those attempting to distinguish between psychotic symptoms and FS. FS and stroke symptoms can also be mistaken for each other, complicating accurate identification.[12-14]

FS treatments, including psychoeducational and psychotherapeutic interventions, demonstrate positive outcomes.[15-19] Accepting the FS diagnosis by patients themselves may be challenging, underscoring the need of repeated psychoeducation to help them embrace the condition.[20] Etiological models, such as the ICM, place an emphasis on psychophysiological mechanisms, particularly sympathetic arousal responses.[9] The implementation of grounding and mindfulness techniques based on understanding the predictive role of the brain can positively impact emotional regulation and symptom management in FS patients.

4. Conclusion

Diagnosing complex conditions, such as FS, stroke, and autoimmune epilepsy is challenging due to overlapping symptoms. In this case, an exhaustive diagnostic process identified FS, underscoring the difficulty of correlating electroencephalographic findings with diverse clinical manifestations. Psychoeducational interventions, followed by structured follow-ups before psychotherapeutic treatment, led to significant improvements in motor performance, cognitive abilities, and self-perception. Importantly, these interventions proved effective even in the absence of immediate access to specialized psychological treatment. This finding suggests that psychoeducation is an essential component of the therapeutic approach for patients with FS. It facilitates patient comprehension of their condition, mitigates stigma, and empowers active participation in their recovery process, as demonstrated in our case.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hospital Ramos Mejía. The patient provided written informed consent to participate in the study.

Consent for publication

Patient consented on the publication of their data.

Availability of data

Data are available from the corresponding author upon reasonable request.

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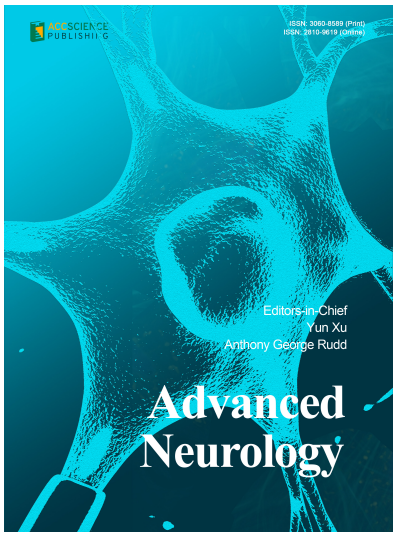

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