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Exploring the influence of BDNF Val66Met gene polymorphism and coping mechanisms on depression, anxiety, and stress among allied health sciences undergraduates

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Abstract: Mental health is influenced by genetic and psychological factors. While higher education supports personal and professional growth, it also poses challenges to student well-being. This research aimed to explore the influence of BDNF Val66Met gene polymorphisms and coping mechanisms on mental health among medical and allied health sciences undergraduates at Universiti Malaysia Sabah. A total of 109 undergraduates completed a series of questionnaires, including a demographic questionnaire, the Depression, Anxiety, Stress Scale-21 (DASS-21), the Brief-Coping Orientation to Problems Experienced (Brief-COPE), and the World Health Organisation Quality of Life – BREF (WHOQOL-BREF). Participants then submitted their saliva samples for gene polymorphism analysis. Results showed that 20.2% of participants had severe to extremely severe symptoms of depression, 43.1% for anxiety, and 15.6% for stress. While homozygous Met allele carriers (Met/Met) had higher mean anxiety and stress scores than Val allele carriers (Val/Val and Val/Met), the differences were not statistically significant. For homozygous Met allele carriers, problem-focused coping showed a negative correlation, whereas emotion-focused coping showed a positive correlation with depression and stress. Avoidant-focused coping was positively predicted by depression among Val allele carriers. Importantly, the Multivariate Analysis of Covariance (MANCOVA) indicated that coping strategies exerted a stronger influence on mental health outcomes than BDNF genotype, even after controlling for demographic variables. Additionally, the psychological quality-of-life subscale significantly predicted mental health outcomes. These findings highlight the need for coping-based interventions to improve students' mental well-being, as well as further research into genetic influences.

Keywords: Mental health; BDNF; Coping mechanism; Quality of life; Undergraduates

1.0 INTRODUCTION

Mental health problems, such as depression, anxiety, and stress, are increasingly common (Kraiss et al., 2024). Stressful life events are recognised as a risk factor for mental health problems, especially during the vulnerable stage of young adulthood (Kraiss et al., 2024; Roth et al., 2023; Zou et al., 2018). According to a meta-analysis that involved 100,187 individuals, the pooled prevalence of depression and anxiety among college students was 33.6% and 39.0%, respectively (Li et al., 2022). The highest prevalence of depression and anxiety was found among medical students (39.4%) (Li et al., 2022).

University students face a range of challenges as they navigate the transition to higher education, such as enrolment in higher education institutions and leaving home (Radeef et al., 2014). These difficulties are often exacerbated by different levels of life stressors, which differ for each individual (Karyotaki et al., 2020). Although a moderate level of stress is a natural aspect of life and can sometimes serve as a motivator, excessive stress can significantly harm one's mental health and well-being (Karyotaki et al., 2020). Research has shown that university students in medical and allied health sciences often face the heaviest workloads compared with their peers in other fields of study. Consequently, medical and allied health sciences students are more susceptible to depression and anxiety due to the demanding nature of the theoretical coursework and clinical practice (Mofatteh, 2021).

Advancements in healthcare services have contributed to an increase in average life expectancy in the past few decades (Vaupel et al., 2019). However, this rise in life expectancy does not necessarily reflect an improvement in the quality of life (Cai et al., 2021). In 1995, the World Health Organisation defined quality of life as an individual's perception of their position in life, which is influenced by cultural and moral values, the environment they live in, and their personal life goals and expectations (World Health Organization, 1995). Mental health issues contribute to a reduced quality of life by hindering individuals' ability to carry out daily tasks and responsibilities (Defar et al., 2023).

Susceptibility to stress varies among individuals, and it is influenced by factors such as genetic vulnerability and coping mechanisms (Salleh, 2008). The diathesis-stress model proposed that each individual possesses some degree of inherent vulnerability, which is the diathesis for developing a certain disorder. The onset of a disorder can then be triggered by stress. However, the intensity of stress required to trigger a disorder is determined by the degree of an individual's inherent vulnerability (Broerman, 2020). Genetic risk factors could be considered as the diathesis (Arnau-Soler et al., 2019). Research on genetic influences on mental health disorders reported that there is a relationship between genotype and the risk of developing mental health disorders, suggesting that for an individual who possesses genetic vulnerability to a mental health disorder, even a low level of stress may easily trigger the development of that particular disorder.

Brain-derived neurotrophic factor (BDNF) plays a crucial role in regulating neuronal activity and synaptic plasticity (Kowiański et al., 2017). The BDNF gene is located on human chromosome 11 and band p13 (Pruunsild et al., 2007). An important variant, known as the BDNF Val66Met polymorphism (rs6265), is a naturally occurring single-nucleotide polymorphism. An alteration at the 5′ promoter region in the pro-BDNF, resulting in the substitution of guanine (G) with adenine (A) at nucleotide position 196, results in the substitution of an amino acid from valine (Val) to methionine (Met) at codon 66 in the BDNF (Faris et al., 2020). The polymorphism has been associated with reduced activity-induced BDNF secretion (Egan et al., 2003; Finan et al., 2018). The reduction in BDNF secretion was reported through the binding of sortilin with the prodomain of BDNF in the methionine region, thus disrupting the release of BDNF into the synapse (Chen et al., 2005; Finan et al., 2018). This explains the findings showing a 29% decrease in activity-dependent BDNF secretion in homozygous Met/Met genotypes compared with homozygous Val/Val and heterozygous Val/Met genotypes (Chen et al., 2006). This highlights the protective role of the Val allele and the increased risk of being homozygous Met at intracellular levels. In addition, the reduction in BDNF secretion is associated with atrophy in the hippocampus and prefrontal cortex (Duman & Monteggia, 2006). Studies reported that Met alleles are associated with bilateral hippocampal volume reduction (Hajek et al., 2012; Pezawas et al., 2004). Brain imaging in healthy controls demonstrated that homozygous Met allele carriers had a smaller hippocampal formation than homozygous Val/Val carriers (Bueller et al., 2006). The Val allele is associated with higher BDNF secretion, which supports neuroplasticity and cognitive function. In contrast, a significantly increased risk for suicide was found among homozygous Met compared to the heterozygous Val/Met and homozygous Val in Caucasian populations (González-Castro et al., 2017). In addition, an increased risk of major depressive disorder was found among men with a homozygous Met allele (Verhagen et al., 2010). Another research also reported that homozygous Met carriers present with higher schizophrenic scores, poorer cognitive function, and lower levels of serum BDNF (Farcas et al., 2023). Furthermore, individuals carrying the homozygous Met allele have a higher risk of developing generalised anxiety disorder (González-Castro et al., 2019) and stress (Al-Hatamleh et al., 2019). Therefore, the presence of the BDNF homozygous Met allele may serve as a potential predictor for the development of mental health problems in individuals (Pathak et al., 2022).

Coping mechanisms refer to the behavioural and psychological strategies individuals use to manage and adapt to stressful circumstances (Al-Dubai et al., 2011). An individual may utilise problem-focused coping strategies, emotion-focused coping strategies, or avoidant strategies when facing stressful situations (Cheng et al., 2021). The use of problem-focused coping strategies to manage stressful life events is associated with a reduced risk of mental health problems (Cheng et al., 2021). whereas the use of emotion-focused coping strategies to manage stressful life events is linked to an increased risk of mental health issues (Cheng et al., 2021; Tomczak-Witych, 2006)Relying on avoidant coping (Hofmann & Hay, 2018), which is a maladaptive behavioural response driven by intense fear and anxiety, is associated with anxiety (Hofmann & Hay, 2018; Poole et al., 2021; Quah et al., 2020) and stress (Allen, 2021).
This study aimed to explore the influences of genes and coping mechanisms on mental health outcomes and quality of life among medical and allied health sciences undergraduates.

2.0 MATERIALS AND METHODS

2.1 Research design and participants

This cross-sectional study was approved by the Medical Ethics Committee of Universiti Malaysia Sabah [approval code: JKEtika 3/20 (12)]. All participants were provided with clear explanations regarding the research objectives and procedures, and written informed consent was obtained prior to participation.

This study was conducted at the Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah (FMHS, UMS), and involved two phases of data collection. In Phase I, questionnaires were distributed via Google Forms, while in Phase II, saliva samples were collected at the laboratory of the Department of Biomedical Sciences, FMHS, UMS. The inclusion criteria were that participants be current undergraduate students enrolled in medical or allied health sciences programs at UMS. Students with a self-reported history of diagnosed mental health conditions or those receiving psychiatric treatment were excluded. The sample size was calculated based on a population of 660 students, a 95% confidence level, a 5% margin of error, and an expected prevalence of 5%, resulting in a minimum required sample size of 66 participants.

A total of 206 undergraduates were recruited through convenience sampling in Phase I, and 109 agreed to provide saliva samples in Phase II. Thus, the final analysis was based on these 109 participants. Of them, 23 (21.1%) were male, and 86 (78.9%) were female, with a mean age of 20.61 years (*SD*=1.35). The majority were from the Medicine program (77.98%), followed by Nursing (11.92%) and Food Science (10.10%). In terms

Table 1. Demographic characteristics

Variables	Categories	n (%)
Age	Years (Mean ± SD)	20.61 ± 1.35
Gender	Male	23 (21.1%)
	Female	86 (78.9%)
Ethnicity	Kadazan-Dusun	45 (41.28%)
	Chinese	21 (19.27%)
	Malay	20 (18.34%)
	Indian	8 (7.34%)
	Bajau	5 (4.59%)
	Bruneian	4 (3.67%)
	Others	6 (5.50%)
Programme	Medicine	85 (77.98%)
	Nursing	13 (11.92%)
	Food Science	11 (10.10%)

of ethnicity, 41.28% were Kadazan-Dusun, 19.27% Chinese, 18.34% Malay, 7.34% Indian, 4.59% Bajau, 3.67% Bruneian, and 5.50% from other ethnic groups (see **Table 1**).

For analytical purposes, participants were categorised into groups based on the Depression, Anxiety, and Stress Scale severity scores. Individuals with severe to extremely severe scores in depression, anxiety, or stress were classified as having severe symptoms, while those with normal, mild, and moderate scores were categorised as normal. These groupings were used to facilitate further statistical analyses.

2.2 Research materials

Demographic data, including age, gender, and educational background, were obtained through a self-administered questionnaire.

Mental health status was measured using the Depression, Anxiety, and Stress Scale–21 (DASS-21), which demonstrated good internal consistency (Cronbach's α=0.87). The DASS-21 consists of three subscales, i.e., depression, anxiety, and stress, each containing seven items. The depression subscale evaluates hopelessness, low self-esteem, and reduced positive emotions; the anxiety subscale assesses physical arousal, musculoskeletal symptoms, situational anxiety, and agitated arousal; while the stress subscale measures tension, agitation, and negative affect. All items are rated on a four-point Likert scale (Al-Hatamleh et al., 2019).

Coping strategies in response to stressful situations were assessed using the Brief-Coping Orientation to Problems Experienced (Brief-COPE) inventory, which showed acceptable internal consistency (Cronbach's α=0.82). This 28-item instrument evaluates three primary coping styles: problem-focused, emotion-focused, and avoidant coping, using a four-point response scale (Wise et al., 2023).

Quality of life was measured using the World Health Organisation Quality of Life–BREF (WHOQOL-BREF), which is a 26-item questionnaire covering four domains: physical health, psychological health, social relationships, and environment. The WHOQOL-BREF demonstrated high internal consistency (Cronbach's α=0.896), with responses rated on a five-point Likert scale (Ilić et al., 2019).

2.3 Buccal cells and DNA extraction

DNA was extracted from buccal cells obtained from participants. Prior to collection, participants were instructed to refrain from eating for at least 30 minutes. On arrival, the saliva collection procedure was explained, after which each participant was provided with a cup of drinking water and a Falcon tube. Participants were asked to gargle with the water for one minute and then expel it into the tube. The collected samples were centrifuged at 3,000 rpm for 5 minutes, and the supernatant was discarded. The resulting mucosal cell pellet was resuspended in 500 µL of phosphate-buffered saline (PBS) and heated at 95 °C for 10 minutes in a heating block to facilitate cell lysis. The samples were then centrifuged again at 3,000 rpm for 5 minutes, and the supernatant was collected for polymerase chain reaction (PCR) analysis.

2.4 Polymerase chain reaction - restriction fragment length polymorphism

The BDNF Val66Met gene polymorphism was analysed using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP). PCR amplification of the BDNF gene was performed in a 25 µL reaction mixture containing 5 µL of DNA template, 1 µL each of 10 µM forward and reverse primers (Forward: 5′-GAGGCTTGACATCATTGGCT-3′; Reverse: 5′-CGTGTACAAGTCTGCGTCCT-3′), 5 µL of 5× colourless GoTaq® Flexi buffer, 2 µL of 25 mM $MgCl_2$ solution, 0.5 µL of dNTPs, and 11.5 µL of nuclease-free water. The PCR cycling conditions consisted of an initial

Table 2. PCR primer sequences and amplification conditions for BDNF Val66Met(rs6265)

Forward primer (5′–3′)	GAGGCTTGACATCATTGGCT
Reverse primer (5′–3′)	CGTGTACAAGTCTGCGTCCT
Amplicon size (bp)	113
Annealing temperature (°C)	60
Restriction enzyme	Eco72I (PmlI)
Digestion fragments (bp)	• Val/Val: 78, 35 • Val/Met: 113, 78, 35 • Met/Met: 113

Note. PCR products were digested with the Eco72I (PmlI) restriction enzyme and visualised on a 3% agarose gel.

denaturation at 95 °C for 3 minutes, followed by 35 cycles of denaturation at 95 °C for 30 seconds, annealing at 60 °C for 30 seconds, and extension at 72 °C for 30 seconds. A final extension step was carried out at 72 °C for 5 minutes (see **Table 2**).

Subsequently, 10 µL of the PCR product was digested with 5 units (0.5 µL) of Eco72I (PmlI) restriction enzyme (New England Biolabs, Massachusetts, USA) in a 20 µL reaction containing 2 µL of 10× Buffer Tango (33 mM Tris-acetate, pH 7.9; 66 mM potassium acetate; 10 mM magnesium acetate; 0.1 mg/mL BSA) and 7.5 µL of distilled water. The mixture was incubated at 37 °C for 16 hours, then inactivated at 65 °C for 20 minutes.

The digested products were separated by electrophoresis on a 3% agarose gel, stained with Fluorosafe (Apical Scientific Sdn. Bhd., Selangor, Malaysia), and run at 100 V for 1 hour in 1× Tris-acetate-EDTA (TAE) buffer. The gel was visualised under ultraviolet light using the ChemiDoc™ Imaging System with Image Lab software (Bio-Rad Laboratories, USA). The BDNF Val66Met polymorphism was identified as three possible genotypes: Val/Val (78 bp and 35 bp fragments), Val/Met (113 bp, 78 bp, and 35 bp fragments), and Met/Met (113 bp fragment).

2.5 Statistical analysis

Data were analysed using IBM SPSS Statistics version 27. For this study, participants were grouped based on a recessive genetic model, comparing individuals with the Met/Met genotype to Val allele carriers (Val/Val and Val/Met) (Liu et al., 2021). This approach was adopted due to small cell counts in the Val/Val genotype group. Genotype frequencies were compared between groups using Pearson's chi-square test. Allele frequencies were calculated from genotype counts and analysed using weighted chi-square tests. Odds ratios (ORs) and 95% confidence intervals (CIs) were analysed using binary logistic regression. In addition, binary logistic regression analysis was conducted to examine the association between BDNF Val66Met genotype and coping strategies with the likelihood of depression, anxiety, and stress. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. Multiple linear regression using the enter method was applied, with all coping mechanism subscales entered simultaneously to examine their predictive relationships with depression, anxiety, and stress. In addition, a Multivariate Analysis of Covariance (MANCOVA) was conducted to evaluate the influence of genotype and coping strategies while controlling for covariates. Two models were tested: 'Model A' included age and gender as covariates, while 'Model B' included age, gender, and coping mechanisms. Finally, Spearman's rho correlation was used to assess the associations between quality of life domains and mental health outcomes. Statistical significance was set at $p<0.05$.

3.0 RESULTS

3.1 Prevalence of depression, anxiety, and stress among medical and allied health sciences undergraduates

The majority of participants were classified within the normal range for all three psychological domains. For depression, 79.8% (*n*=87) of participants were categorised as normal, while 20.2% (*n*=22) were classified as having severe symptoms. In contrast, anxiety showed a higher prevalence, with 56.9% (*n*=62) of participants categorised as normal, whereas 43.1% (*n*=47) had severe symptoms. For stress, most participants were normal (84.4%, *n*=92), with a smaller proportion (15.6%, *n*=17) experiencing severe symptoms (see **Table 3**). These findings indicate that

Table 3. Prevalence of depression, anxiety and stress among medical and allied health sciences undergraduates

Severity Level	Depression % (n)	Anxiety % (n)	Stress % (n)
Normal	44.0 (*n*=48)	22.9 (*n*=25)	42.2 (*n*=46)
Mild	12.8 (*n*=14)	8.3 (*n*=9)	17.4 (*n*=19)
Moderate	22.9 (*n*=25)	25.7 (*n*=28)	24.8 (*n*=27)
Normal (Normal–Moderate)	79.8 (*n*=87)	56.9 (*n*=62)	84.4 (*n*=92)
Severe	9.2 (*n*=10)	11.0 (*n*=12)	9.2 (*n*=10)
Extremely Severe	11.0 (*n*=12)	32.1 (*n*=35)	6.4 (*n*=7)
Severe (Severe–Extremely Severe Combined)	20.2 (*n*=22)	43.1 (*n*=47)	15.6 (*n*=17)

Note. The normal category includes participants who obtained scores from normal to moderate levels in DASS-21, and the severe category includes participants who obtained scores from severe to extremely severe levels in DASS-21.

anxiety was the most prevalent psychological issue among the participants, followed by depression and stress.

3.2 BDNF Val66Met genotype and allele distribution analysis

Based on the gel electrophoresis profiles, three genotypes of the BDNF Val66Met polymorphism were identified, i.e., homozygous Met/Met (113 bp), homozygous Val/Val (78 bp and 35 bp), and heterozygous Val/Met (113 bp, 78 bp, and 35 bp) (**Figure 1**). Among the participants, the Met/Met genotype was the most common (56.9%, *n*=62), followed by Val/Met (37.6%, *n*=41) and Val/Val (5.5%, *n*=6). Correspondingly, allele frequency analysis showed that the Met allele was more prevalent (75.7%) compared to the Val allele (24.3%). A recessive genetic model was applied for subsequent analysis. Individuals with either Val/Val or Val/Met genotypes were grouped as Val allele carriers, while those with the Met/Met genotype were classified as Met allele carriers.

3.2.1 Genotype frequencies and association

There were no significant differences in genotype distribution observed between normal and severe groups for depression (χ^2=2.38, *p*=0.304), anxiety (χ^2=4.65, *p*=0.098), and stress (χ^2=1.19, *p*=0.552). Notably, the Val/Val genotype was absent in all severe groups (see **Table 4**). Logistic regression analysis using a recessive genetic model (Met/Met vs. Val/Val + Val/Met) revealed no significant association between BDNF genotype and depression (OR=2.15, 95% CI: 0.71–6.51, *p*=0.174), anxiety (OR=1.35, 95% CI: 0.58–3.13, *p*=0.484), or stress (OR=1.04, 95% CI: 0.33–3.29, *p*=0.941) (see **Table 5**).

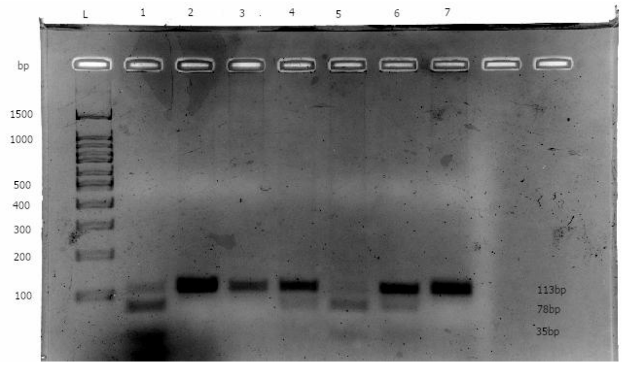

Figure 1. Representative figure of the BDNF Val66Met polymorphism DNA electrophoresis. L: 100 bp DNA ladder; Lane 1: Val/Val; Lane 2: Met/Met; Lane 3: Met/Met; Lane 4: Val/Met; Lane 5: Val/Val; Lane 6: Val/Met; Lane 7: Met/Met. **Note.** Val/Val: 78 bp, 35 bp; Val/Met: 113 bp, 78 bp, 35 bp; Met/Met: 113 bp

Table 4. Genotype and allele distributions and associations of BDNF Val66Met with mental health outcomes

Outcomes	Category	Genotypes				Alleles		
		Val/Val	Val/Met	Met/Met		Val	Met	
Depression	Normal n (%)	6 (6.9)	34 (39.1)	47 (54.0)		46 (26.4)	128 (73.6)	
	Severe n (%)	0 (0.0)	7 (31.8)	15 (68.2)		7 (15.9)	37 (84.1)	
	χ^2 (*df*)				2.38 (2)			2.12 (1)
	p				0.304			0.146
	OR (95% CI)				—			1.90 (0.79–4.56)
Anxiety	Normal n (%)	6 (9.5)	23 (36.5)	34 (54.0)		35 (27.8)	91 (72.2)	
	Severe n (%)	0 (0.0)	18 (39.1)	28 (60.9)		18 (19.6)	74 (80.4)	
	χ^2 (*df*)				4.65			1.95 (1)
	p				0.098			0.163
	OR (95% CI)				—			1.58 (0.83–3.02)
Stress	Normal n (%)	6 (6.5)	34 (37.0)	52 (56.5)		46 (25.0)	138 (75.0)	
	Severe n (%)	0 (0.0)	7 (41.2)	10 (58.8)		7 (20.6)	27 (79.4)	
	χ^2 (*df*)				1.19			0.30 (1)
	p				0.552			0.582
	OR (95% CI)				—			1.29 (0.53–3.15)

Note. *p-values* for genotype and allele distributions were obtained using Pearson chi-square tests. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using binary logistic regression.

3.2.2 Allele frequencies

Allele frequency analysis revealed no significant differences between groups. Allele frequencies were calculated based on genotype counts, and comparisons were performed using chi-square tests with weighted allele data. Allele frequency analysis revealed no significant differences between normal and severe groups for depression ($\chi^2(1)=2.12$, $p=.146$), anxiety ($\chi^2(1)=1.95$, $p=.163$), and stress ($\chi^2(1)=0.30$, $p=.582$). Logistic regression analysis indicated that the Met allele was not significantly associated with depression (OR=1.90, 95% CI [0.79, 4.56], $p=.146$), anxiety (OR=1.58, 95% CI [0.83, 3.02], $p=.163$), or stress (OR=1.29, 95% CI [0.53, 3.15], $p=.582$) (see **Table 4**).

3.3 BDNF Val66Met gene polymorphism and mental health

An independent samples *t*-test was conducted to compare depression, anxiety, and stress scores between homozygous Met allele carriers and Val allele carriers (Val/Val and Val/Met). For depression, there was no statistically significant difference between Val allele carriers ($M=12.94$, $SD=10.21$) and homozygous Met allele carriers ($M=12.06$, $SD=9.82$), $t(107)=0.45$, $p=0.653$. For anxiety, there was no statistically significant difference between Val allele carriers ($M=13.87$, $SD=9.42$) and homozygous Met allele carriers ($M=15.13$, $SD=9.63$), $t(107)=-0.68$, $p=0.497$. For stress, there was no statistically significant difference between Val allele carriers ($M=15.74$, $SD=9.95$) and homozygous Met allele carriers ($M=17.03$, $SD=9.02$), $t(107)=-0.71$, $p=0.482$ (**Figure 2**). Overall, these results indicate that there were no significant differences in depression, anxiety, or stress scores between homozygous Met allele carriers and Val allele carriers.

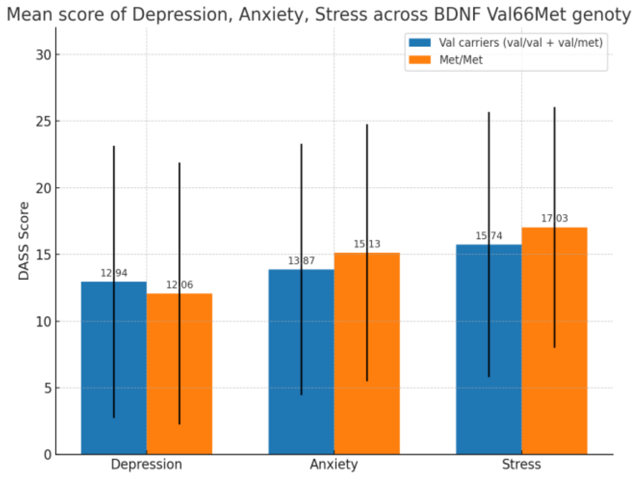

Figure 2. The mean score of depression, anxiety, and stress across BDNF Val66Met genotypes.

3.4 Logistic regression analysis of BDNF Val66Met genotype and coping strategies on mental health outcomes

For logistic regression analysis, depression, anxiety, and stress were dichotomised based on DASS-21 severity categories. Participants with severe-to-extremely severe scores were classified as severe, whereas participants with normal-to-moderate scores were classified as normal (see **Table 3**). Binary logistic regression analyses were conducted to examine the effects of BDNF Val66Met polymorphism and coping strategies (problem-focused coping, emotion-focused coping, and avoidant coping) on anxiety, depression, and stress (see **Table 6**). All continuous predictors were mean-centred prior to analysis, and interaction terms between BDNF genotype and coping variables were included to assess moderation effects. Gender was included as a covariate.

Table 5. Association between BDNF Val66Met polymorphism (recessive model) and mental health outcomes

Outcomes	Genetic Model	OR (95% CI)	*p*
Depression	Val/Val + Val/Met (Reference)	Reference	—
	Met/Met	2.15 (0.71–6.51)	.174
Anxiety	Val/Val + Val/Met (Reference)	Reference	—
	Met/Met	1.35 (0.58–3.13)	.484
Stress	Val/Val + Val/Met (Reference)	Reference	—
	Met/Met	1.04 (0.33–3.29)	.941

Note. OR=odds ratio; CI=confidence interval. The recessive genetic model compares Met/Met homozygotes with Val allele carriers (Val/Val + Val/Met), which were used as the reference group. Odds ratios were obtained from binary logistic regression analyses.

Table 6. Logistic Regression Analyses of BDNF Val66Met polymorphism, coping mechanisms, genotypes x coping mechanism and gender

Categories	Variables	Depression OR (95% CI)	p	Anxiety OR (95% CI)	p	Stress OR (95% CI)	p
Genotypes	BDNF genotype	1.91 (0.55–6.65)	0.311	1.34 (0.57–3.15)	0.497	1.74 (0.40–7.57)	0.463
Coping Mechanism	Problem-Focused coping	0.94 (0.70–1.27)	0.695	0.99 (0.82–1.21)	0.948	1.15 (0.81–1.62)	0.437
	Emotion-Focused coping	1.00 (0.77–1.29)	0.984	1.00 (0.83–1.20)	0.999	1.08 (0.81–1.43)	0.615
	Avoidant coping	1.24 (0.93–1.66)	0.147	1.21 (0.97–1.50)	0.090	1.31 (0.94–1.82)	0.116
Genotypes X Coping Mechanism	BDNF × Problem-Focused coping	0.84 (0.59–1.19)	0.321	0.86 (0.67–1.11)	0.247	0.77 (0.52–1.15)	0.201
	BDNF × Emotion-Focused coping	1.16 (0.85–1.58)	0.344	1.13 (0.90–1.43)	0.292	1.04 (0.74–1.46)	0.836
	BDNF × Avoidant coping	0.93 (0.66–1.32)	0.691	0.94 (0.71–1.24)	0.659	0.83 (0.56–1.22)	0.337
Gender	Gender	0.55 (0.16–1.91)	0.346	0.64 (0.23–1.81)	0.402	0.42 (0.12–1.53)	0.190

Note. OR=Odds Ratio; CI=Confidence Interval. All predictors were mean-centred prior to analysis. No interaction terms were statistically significant.

3.4.1 Depression

The logistic regression model for depression was statistically significant, $\chi^2(8)=16.84$, $p=0.032$, accounting for approximately 22.6% of the variance (Nagelkerke $R^2=0.226$). The Hosmer–Lemeshow test indicated good model fit, $\chi^2(8)=4.74$, $p=0.785$. BDNF genotype was not significantly associated with depression (OR=1.91, 95% CI [0.55, 6.65], p=0.311). Similarly, coping strategies were not significant predictors, including problem-focused coping (OR=0.94, 95% CI [0.70, 1.27], p=0.695), emotion-focused coping (OR=1.00, 95% CI [0.77, 1.29], p=0.984), and avoidant coping (OR=1.24, 95% CI [0.93, 1.66], p=0.147). Interaction effects between BDNF genotype and coping strategies were not statistically significant. Specifically, the interaction between genotype and problem-focused coping (OR=0.84, 95% CI [0.59, 1.19], p=0.321), emotion-focused coping (OR=1.16, 95% CI [0.85, 1.58], p=0.344), and avoidant coping (OR=0.93, 95% CI [0.66, 1.32], p=0.691) were not significant. Gender was also not significantly associated with depression (OR=0.55, 95% CI [0.16, 1.91], p=0.346). These findings suggest that neither genotype, coping strategies, nor their interaction significantly predicts depression.

3.4.2 Anxiety

The logistic regression model for anxiety approached statistical significance, $\chi^2(8)=15.27$, $p=0.054$, accounting for approximately 17.6% of the variance (Nagelkerke $R^2=.176$). The Hosmer–Lemeshow test indicated good model fit, $\chi^2(8)=3.25$, $p=0.918$. BDNF genotype was not significantly associated with anxiety (OR=1.34, 95% CI [0.57, 3.15], p=0.497). Coping strategies were also not significant predictors, including problem-focused coping (OR=0.99, 95% CI [0.82, 1.21], p=0.948), emotion-focused coping (OR=1.00, 95% CI [0.83, 1.20], p=0.999), and avoidant coping (OR=1.21, 95% CI [0.97, 1.50], p=0.090). Interaction effects between BDNF genotype and coping strategies were not statistically significant. Specifically, the interaction between genotype and problem-focused coping (OR=0.86, 95% CI [0.67, 1.11], p=0.247), emotion-focused coping (OR=1.13, 95% CI [0.90, 1.43], p=0.292), and avoidant coping (OR=0.94, 95% CI [0.71, 1.24], p=0.659) were not significant. Gender was not significantly associated with anxiety (OR=0.64, 95% CI [0.23, 1.81], p=0.402). These findings indicate that neither genotype, coping strategies, nor their interaction significantly predicts anxiety.

3.4.3 Stress

The logistic regression model for stress approached statistical significance, $\chi^2(8)=15.10$, $p=0.057$, accounting for approximately 22.3% of the variance (Nagelkerke $R^2=.223$). The Hosmer–Lemeshow test indicated good model fit, $\chi^2(8)=5.05$, $p=0.752$. BDNF genotype was not significantly associated with stress (OR=1.74, 95% CI [0.40, 7.57], p=0.463). Coping strategies were also not significant predictors, including problem-focused coping (OR=1.15, 95% CI [0.81, 1.62], p=0.437), emotion-focused coping (OR=1.08, 95% CI [0.81, 1.43], *p*=0.615), and avoidant coping (OR=1.31, 95% CI [0.94, 1.82], *p*=0.116). Interaction effects between BDNF genotype and coping strategies were not statistically significant. Specifically, the interaction between genotype and problem-focused coping (OR=0.77, 95% CI [0.52, 1.15], *p*=0.201), emotion-focused coping (OR=1.04, 95% CI [0.74, 1.46], *p*=0.836), and avoidant coping (OR=0.83, 95% CI [0.56, 1.22], *p*=0.337) were not significant. Gender was not significantly associated with stress (OR=0.42, 95% CI [0.12, 1.53], *p*=0.190). These findings indicate that neither genotype nor coping strategies, nor their interaction, significantly predict stress.

3.4.4 Summary of logistic regression analysis

Across all models, BDNF Val66Met polymorphism, coping mechanisms, or gender were not significantly associated with depression, anxiety, or stress. Additionally, no significant interaction effects were observed between BDNF genotype and coping mechanisms. Given the relatively small sample size, the study may have been underpowered to detect interaction effects. Additionally, no correction for multiple testing was applied to the interaction analyses due to their exploratory nature, and the results should be interpreted with caution.

3.5 Coping mechanism prediction on mental health

3.5.1 Multiple linear regression analysis of BDNF Val66Met Val allele and coping mechanism

Multiple linear regression was computed to assess the relationship between coping mechanisms and depression, anxiety, and stress among allied health sciences undergraduates with the BDNF Val66Met Val allele carriers. Coping strategies accounted for 26.7% of the variance in depression ($F(3, 43)=5.23$, $p=0.004$), 17.5% of the variance in anxiety ($F(3, 43)=3.05$, $p=0.039$) and 18.7% of the variance in stress ($F(3, 43)=3.30$, $p=0.029$) for Val allele carriers. Avoidant coping was a significant predictor of depression (β=0.364, *p*=0.044), suggesting that avoidance-based strategies may worsen depression among Val allele carriers (see **Table 7**).

Table 7. Multiple linear regression of BDNF Val66Met Val allele and homozygous Met allele with coping mechanisms

Alleles	**Outcome**	**Predictor**	**B**	**SE B**	**β**	**t**	***p***
Val Allele	Depression	Problem - Focused Coping	-0.643	0.393	-0.291	-1.636	0.109
		Emotion - Focused Coping	0.385	0.371	0.226	1.036	0.306
		Avoidant Coping	0.889	0.429	0.364	2.075	0.044
	Anxiety	Problem - Focused Coping	-0.341	0.385	-0.168	-0.887	0.38
		Emotion - Focused Coping	0.379	0.363	0.242	1.044	0.302
		Avoidant Coping	0.597	0.419	0.265	1.424	0.162
	Stress	Problem - Focused Coping	-0.157	0.403	-0.073	-0.389	0.699
		Emotion - Focused Coping	0.361	0.381	0.218	0.948	0.348
		Avoidant Coping	0.689	0.44	0.289	1.565	0.125
Homozygous Met Allele	Depression	Problem - Focused Coping	-1.418	0.31	-0.684	-4.582	<0.001
		Emotion - Focused Coping	1.034	0.287	0.601	3.606	0.001
		Avoidant Coping	0.363	0.333	0.139	1.088	0.281
	Anxiety	Problem - Focused Coping	-0.637	0.345	-0.313	-1.847	0.07
		Emotion - Focused Coping	0.618	0.319	0.366	1.935	0.058
		Avoidant Coping	0.336	0.371	0.131	0.906	0.369
	Stress	Problem - Focused Coping	-0.951	0.31	-0.499	-3.07	0.003
		Emotion - Focused Coping	0.781	0.287	0.494	2.723	0.009
		Avoidant Coping	0.249	0.333	0.104	0.748	0.457

Note. B=unstandardized coefficient; SE=standard error; β=standardised coefficient. *p<0.05 indicates statistical significance.*

3.5.2 Multiple linear regression analysis of BDNF Val66Met homozygous Met allele and coping mechanism

Multiple linear regression was computed to assess the relationship between coping mechanisms and depression, anxiety, and stress among allied health sciences undergraduates with the BDNF Val66Met homozygous Met allele carriers. Coping strategies accounted for 31.7% of the variance in depression [F (3, 58)=8.96, p<0.001], 11.8% of the variance in anxiety [F(3, 58)=2.59, p > 0.05], and 19.0% of the variance in stress [F (3, 58)=4.52, p=0.006]. Problem-focused coping was a significant negative predictor of depression (β=–0.684, p<0.001) and stress (β=–0.499, p=0.003), suggesting that it may be a protective factor against psychological distress. In contrast, emotion-focused coping was a positive predictor of depression (β=0.601, p=0.001) and stress (β=0.494, p=0.009), indicating that reliance on emotion-focused coping may contribute to increased distress among homozygous Met allele carriers (see **Table 7**).

3.6 Association between BDNF Val66Met genotype and mental health outcomes

3.6.1 Multivariate analysis of covariance of BDNF Val66Met and mental health with age and gender as covariates (MODEL A)

A MANCOVA, categorised as Model A, was conducted to examine differences in depression, anxiety, and stress across BDNF Val66Met genotypes (Val/Val + Val/Met vs Met/Met), controlling for age and gender (see **Table 8**). Assumptions were met (Box's M=5.99, p=0.446; Levene's tests for all DVs ps > 0.29). The multivariate test was not significant for genotype [Pillai's trace=0.013, F(3, 103)=0.46, p=0.714, partial η^2=0.013]. Age showed a significant multivariate effect [Pillai's trace=0.075, F(3, 103)=2.80, p=0.044], whereas gender did not [Pillai's trace=0.027, F(3, 103)=0.95, p=0.421]. Univariate follow-ups showed no genotype differences for depression, anxiety, or stress (all ps ≥ 0.600).

3.6.2 Multivariate analysis of covariance of BDNF Val66Met homozygous and mental health with age, gender, and coping mechanisms as covariates (MODEL B)

A MANCOVA, which was categorised as Model B, was conducted to examine differences in depression, anxiety, and stress across BDNF Val66Met genotypes (Val/Val + Val/Met vs Met/Met), including problem-focused coping, emotion-focused coping, avoidant coping, age, and gender as covariates (see **Table 8**). Assumptions were met (Box's M=5.99, p=0.446; Levene's tests ps > 0.22). Genotype was not significant at the multivariate level [Pillai's trace=0.016, F(3, 100)=0.56, p=.644, partial η^2=0.016]. In contrast, problem- focused coping [Pillai's=0.186, F(3, 100)=7.61, p<0.001] and emotion-focused coping [Pillai's=0.126, F(3, 100)=4.80, p=0.004] showed significant multivariate effects. Univariate tests mirrored this pattern: higher problem-focused and emotion-focused coping were associated with lower depression, anxiety, and stress, whereas genotype remained non-significant across all mental health outcome variables.

Table 8. Multivariate Analysis of Covariance of depression, anxiety, and stress by BDNF Val66Met genotype, controlling for age and gender (Model A), controlling for age, gender and coping mechanisms (Model B)

	Effect	Pillai's Trace	F	Hyp *df*	Error *df*	*p*
Model A	Age	0.075	2.80	3	103	0.044
	Gender	0.027	0.95	3	103	0.421
	Genotype (BDNF Val/Val + Val/Met vs Met/Met)	0.013	0.46	3	103	0.714
Model B	Problem-Focused Coping	0.186	7.61	3	100	< 0.001
	Emotion-Focused Coping	0.126	4.80	3	100	0.004
	Avoidant Coping	0.037	1.28	3	100	0.284
	Age	0.055	1.93	3	100	0.130
	Gender	0.055	1.94	3	100	0.128
	BDNF Genotype (Val/Val + Val/Met vs Met/Met)	0.016	0.56	3	100	0.644

Note. Multivariate tests are based on Pillai's Trace. Dependent variables are depression, anxiety, and stress.

Table 9. *Spearman's rho correlations of depression, anxiety and stress with WHOQOL-BREF domains*

Variable	Depression	Anxiety	Stress
WHO Physical Health	-0.475**	-0.301**	-0.324**
WHO Psychological	-0.574**	-0.381**	-0.387**
WHO Social Relationship	-0.408**	-0.174	-0.262**
WHO Environment	-0.451**	-0.328**	-0.302**

Note. Values are Spearman's rho correlation coefficients. ***p*<0.01

3.6.3 MANCOVA Analysis of Model A and B

Across both models, BDNF genotype was not significantly associated with depression, anxiety, or stress. The inclusion of coping mechanisms in Model B did not change the non-significant genotype findings. However, it revealed that problem-focused and emotion-focused coping were predictors of mental health outcomes. These results suggest that in this study, coping mechanisms exert a stronger influence on mental health outcomes than BDNF genotype, even after controlling for demographic variables.

3.7 Quality of life and mental health

A Spearman's rank-order correlation was used to examine the associations between WHOQOL-BREF domains and mental health outcomes (see **Table 9**). Depression was significantly negatively correlated with physical health (ρ=–0.475, *p*<0.001), psychological well-being (ρ=–0.574, *p*<0.001), social relationships (ρ=–0.408, *p*<0.001), and environment (ρ=–0.451, *p*<0.001), indicating that higher depression scores were associated with poorer perceived quality of life in all domains. Anxiety showed significant negative correlations with physical health (ρ=–0.301, *p*=0.001), psychological (ρ=–0.381, *p*<0.001), and environment (ρ=–0.328, *p*=0.001), except social relationships (ρ=–0.174, *p*=0.071). Stress was significantly negatively correlated with physical health (ρ=–0.324, *p*=0.001), psychological well-being (ρ=–0.387, *p*<0.001), social relationships (ρ=–0.262, *p*=0.006), and environment (ρ=–0.302, *p*=0.001). These results suggest that a poorer quality of life is consistently related to higher depression, anxiety, and stress levels.

4.0 DISCUSSION

Mental health is a significant public health concern, especially among university undergraduates. University students in healthcare-related fields commonly experience symptoms of depression, anxiety, and stress, with around 20% of students presenting severe or extremely severe levels of mental health problems (Freitas et al., 2022). Similarly, in this study, 20.2% of medical and allied health sciences undergraduates at UMS demonstrated severe to extremely severe symptoms of depression, 43.1% for anxiety, and 15.6% for stress, thereby supporting the hypothesis that mental health problems are prevalent among these students. Anxiety emerged as the most prevalent issue, potentially because students may not fully understand the academic and practical demands of their studies before starting university (Mofatteh, 2021). Although normal levels of anxiety promote learning effectiveness, excessive anxiety decreases learning interest and leads to poorer academic performance (Thandevaraj et al., 2021).

The mental health outcome scores of undergraduates at UMS were higher than those reported in previous studies in Malaysia, likely because data collection was conducted during the COVID-19 pandemic in 2022. Before the pandemic in Malaysia, the prevalence of severe to extremely severe depression, anxiety, and stress was 5.75%, 33.3%, and 3.8% among medical undergraduates (Al-Hatamleh et al., 2019) and 11.1%, 46.1%, and 5.8% among allied health sciences undergraduates, respectively (Fauzi et al., 2021). In contrast, studies conducted after the COVID-19 outbreak reported higher prevalence rates of depression symptoms (35.9%), anxiety symptoms (40.7%), and stress (53%) (Lakhan et al., 2020; Li et al., 2022).

Previous studies have proposed that individuals carrying the homozygous Met allele of the BDNF Val66Met polymorphism are more susceptible to depression, anxiety, and stress. They have been reported to exhibit poorer cognitive function (Han et al., 2020; Yao et al., 2023) and lower serum BDNF levels (Farcas et al., 2023). The Met allele has also been found to be more prevalent in Asian population compared to Caucasians (Ai et al., 2019; Liu et al., 2021), which is consistent with our study population, where the frequency of homozygous Met carriers was higher than that of Val/Met and Val/Val genotypes. Although several studies suggest an association between the BDNF Val66Met polymorphism and depression (Rabago-Barajas et al., 2025), anxiety (González-Castro et al., 2019), and stress (Al-Hatamleh et al., 2019), the overall findings remain inconsistent.

Some recent studies report no association with major depressive disorder (Ramawat et al., 2024) or other mental health outcomes (Wang et al., 2023). In the present study, participants were grouped as homozygous Met allele carriers (Met/Met) versus Val allele carriers (Val/Val and Val/Met) (Liu et al., 2021); similarly, no direct association was found between genotype and mental health outcomes. This absence of a genotype effect aligns with meta-analyses reporting inconsistent associations between BDNF Val66Met and mental health outcomes (Wang et al., 2023).

Both intrinsic factors, such as genetic variation, and extrinsic factors, including lifestyle habits, environmental conditions, and academic demands influence mental health outcomes (Mofatteh, 2021; Uher & Zwicker, 2017; Wang, 2025). However, the influence of genetic and environmental factors varies across different mental health outcomes (Uher & Zwicker, 2017). BDNF regulates neuroplasticity and synaptic function (Kowiański et al., 2017). The BDNF Val66Met polymorphism affects activity-dependent secretion of BDNF; the reduction of BDNF secretion may influence neural plasticity in brain regions such as the hippocampus and prefrontal cortex (Kowiański et al., 2017), thus potentially affecting stress reactivity and emotional regulation (Notaras et al., 2015; Shan et al., 2024). Consequently, individuals carrying the Met allele may exhibit differences in stress sensitivity or emotional reactivity at a neurobiological level. (Limone & Toto, 2022)

Theoretically, the BDNF Val66Met polymorphism could affect an individual's vulnerability to mental health distress (Notaras et al., 2015; Shan et al., 2024). However, in the present study, no significant associations were observed between BDNF Val66Met genotype or allele frequencies with depression, anxiety, and stress. The possible explanation is that the study population, consisting of medical and health sciences students, is exposed to substantial external stressors (Hill et al., 2018). These extrinsic factors may exert a stronger and more immediate influence on mental health outcomes than genetic predisposition. Although the Met allele appeared more frequent in the case groups, these differences did not reach statistical significance. This suggests that the BDNF Val66Met polymorphism may have a limited effect on mental health outcomes among the research participants. In addition, the absence of the Val/Val genotype in the severe group and the relatively small sample size may have reduced the statistical power to detect potential genetic effects. The lack of significant genotype and allele associations suggests that coping mechanisms may play a more prominent role than genetic variation in influencing mental health outcomes within this population.

This study highlighted the critical role of coping mechanisms in shaping students' mental health outcomes. Problem-focused coping emerged as the most protective strategy, consistent with previous studies showing its association with a reduced risk of depression and stress (Karyotaki et al., 2020). Among homozygous Met allele carriers, lower use of problem-focused coping and greater reliance on emotion-focused coping were significant predictors of higher depression and stress scores. This finding aligns with earlier research indicating that emotion-focused coping, often linked with maladaptive rumination and negative thought patterns, is predictive of depression (Caldwell et al., 2013). Avoidance was associated with depressive symptoms among Val allele carriers (Haskell et al., 2020). However, no significant interaction was observed between coping strategies and BDNF genotype, suggesting that this relationship is independent of genetic variation. This suggests that coping mechanisms play an important role in mental health outcomes, independent of BDNF genotype. The MANCOVA results further reinforce this interpretation. Across both models, the BDNF Val66Met genotype was not significantly associated with depression, anxiety, or stress, even when demographic factors and coping mechanisms were controlled. This is consistent with meta-analyses reporting inconsistent associations between the BDNF Val66Met polymorphism and mental health outcomes (Wang et al., 2023). Instead, coping styles, particularly problem-focused and emotion-focused coping, emerged as stronger predictors of mental health outcomes. These findings suggest that behavioural and psychosocial factors may exert a more immediate and modifiable impact on undergraduates' mental health than genetic predisposition alone. In the genotype and coping mechanisms interaction analysis, the absence of significant interaction effects may be attributed to limited statistical power to detect gene–environment interactions.

Mental health is a crucial determinant of quality of life as it can negatively affect daily functioning, academic performance, and social relationships. In this study, a negative correlation was observed between the psychological subscales and mental health outcomes, indicating that individuals with higher scores in quality of life tended to report lower levels of depression, anxiety, and stress. These findings are consistent with previous research showing that depression (Freitas et al., 2023; Li et al., 2020), anxiety (Jenkins et al., 2020), and stress (Freitas et al., 2023) are linked to a poorer quality of life (Freitas et al., 2023). Additionally, a better quality of life has been associated with lower perceived stress, particularly among undergraduate students in allied health sciences (Alkatheri et al., 2019). University students experience multiple stressors, including academic workload, financial concerns, social adjustments, and uncertainty about the future, all of which can influence their mental health and overall quality of life (Liu et al., 2019). Given these challenges, interventions that promote effective stress management and coping strategies are essential to improving mental health and enhancing the quality of life in this population.

4.1 Limitation

This study has several limitations that should be considered when interpreting the findings. First, the sample was ethnically heterogeneous, and allele frequencies of the BDNF Val66Met polymorphism may vary across different ancestry groups. In addition, the differences in both allele frequencies and mental health outcomes measured across ethnic groups may have influenced the observed associations. Another limitation of this study is the low number of individuals with the homozygous Val genotype, which may have reduced the statistical power to detect genotype effects and gene–environment interactions. This is especially relevant for the interaction analyses, which typically require larger sample sizes. Therefore, the generalisability of the findings may be restricted (Farcas et al., 2023).

5.0 CONCLUSIONS

Although no significant associations were found between the BDNF Val66Met polymorphism and depression, anxiety, or stress, coping mechanisms emerged as stronger predictors of psychological outcomes. Maladaptive coping increased vulnerability to poorer mental health, while effective coping enhanced well-being and quality of life. These findings suggest that in young adults, coping mechanisms may exert greater influence on mental health outcomes than a single genetic variant. When coping mechanisms are included as covariates, the association between genotype and mental health outcomes remained non-significant. This highlights coping mechanisms as a potential mediating mechanism linking genetic susceptibility with psychological outcomes. Overall, this study underscores the importance of incorporating coping-focused interventions into mental health strategies for undergraduates, and future research with larger, more diverse samples should further explore gene–environment–coping interactions.

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Ethics statement

The ethics approval for this study was obtained from the Medical Ethics Committee of Universiti Malaysia Sabah [JKEtika 3/20 (12)]. Informed consent for sample collection was obtained from the participant. The authors took ethical concerns into consideration when gathering data and ensured that information obtained from respondents was utilised only for research purposes.

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