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BDNF gene methylation is related to psychological quality of life in police officers

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ABSTRACT

Background: Quality of life (QoL) is a fundamental factor that affects overall health, and its decline is associated with physical and mental illnesses. Studies indicate a significant reduction in the QoL due to the work activities of police officers. The brain-derived neurotrophic factor (BDNF) is associated with neuronal maintenance, memory, and brain plasticity. This gene is epigenetically regulated and undergoes methylation changes in response to environmental pressures to which the individual is exposed.
Purpose: This study aimed to assess the association between *BDNF* gene methylation and QoL in police officers.
Methods and results: A sample of 166 police officers was recruited to assess their QoL, sociodemographic and lifestyle factors, depression, and *BDNF* exon IV *DNA* methylation using pyrosequencing. Generalized linear models multivariate analyses were used to investigate the association between peripheral blood DNA methylation of the *BDNF* gene and QoL after adjusting for confounding factors. The findings indicated that a better psychological QoL in police officers was associated with lower levels of methylation in the regulatory region of *BDNF* exon IV.
Conclusion: The results of this study suggest that *BDNF* gene methylation is associated with the QoL in the psychological domain of police officers, indicating that individuals exposed to the same environmental pressure, such as police activity, exhibit different responses in methylation levels and possibly different adaptive markers in *BDNF* that reflect QoL.

Abbreviations: BDNF, Brain-derived neurotrophic factor; CpG, Cytosine-phosphate-Guanine site; CREB, Cyclic AMP-responsive element-binding protein; DASS-21, Depression, Anxiety, and Stress Scale-21; DNA, Deoxyribonucleic Acid; GzLM, Generalized Linear Model; HPA, Hypothalamus–pituitary–adrenal axis; IQR, Interquartile range; PCR, Polymerase Chain Reaction; QoL, Quality of Life; SPSS, Statistical Package for the Social Sciences; WC, Waist circumference; WHO, World Health Organization; WHOQOL-BREF, World Health Organization Quality of Life Brief Version.

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1. Introduction

According to the World Health Organization (WHO), quality of life (QoL) is defined as an individual's perception of their position in life in relation to their goals, expectations, standards, and concerns (THE WHOQOL GROUP, 1998). It is a broad concept encompassing physical health, psychological state, social relationships, and interactions with the environment (Kaplan and Ries, 2007). Studies have indicated a close relationship between QoL and psychiatric disorders (Talıbov et al., 2024), cardiovascular diseases (Boehm and Kubzansky, 2012; DuBois et al., 2015), and high stress levels (Al-Smadi et al., 2017). Consequently, assessing QoL can be a useful tool for the early detection of diseases (Sagayadevan et al., 2019).

For police officers, QoL is often compromised by the stressful nature of their profession. The prevalence of stress-related conditions and psychiatric disorders is significantly higher in this population compared to other occupational groups (van der Velden et al., 2013). Chronic exposure to these occupational stressors is associated with both physical and mental health (Leino et al., 2011), which may be reflected in a substantial decline in QoL (Alexopoulos et al., 2014; Lipp et al., 2017). Despite the well-documented psychosocial impact, the biological mechanisms through which this burden translates into physiological and epigenetic changes remain an essential field of investigation.

In this context, the Brain-derived neurotrophic factor (BDNF) stands out as a key neurotrophin for neuronal survival, synaptic plasticity, and cognition (Azman and Zakaria, 2022; Yang et al., 2020). Evidence shows that BDNF expression is highly sensitive to stress. Specifically, chronic exposure to stressors has been linked to increased DNA methylation in specific promoter regions, which is often associated with lower BDNF levels in individuals with depression and anxiety (Persaud and Cates, 2022; Ikegame et al., 2013; Chen and Chen, 2017). Furthermore, clinical studies have reported significantly lower plasma concentrations of BDNF in patients with mood disorders (D'Addario et al., 2013; Fuchikami et al., 2011), underscoring its relevance in neurobiological health research (Park and Poo, 2013; Fuchikami et al., 2010; Makhathini et al., 2017).

The literature suggests that *BDNF* methylation is associated with regulatory processes that may relate to neural plasticity and psychological well-being (Yang et al., 2020). In high-stress occupational environments, such as military policing, chronic exposure to stressors is often accompanied by persistent epigenetic changes potentially related to reduced neural resilience (Miao et al., 2020; Duman and Monteggia, 2006). Therefore, QoL in these professionals should be interpreted not merely as a transient state of well-being, but as a complex indicator reflecting long-term neurobiological adjustments and the physiological cost of cumulative occupational stress.

Despite the growing understanding of how environmental pressures shape the epigenome, investigations into these regulatory processes within high-risk occupational groups remain scarce. Therefore, this study aimed to evaluate the association between DNA methylation at the *BDNF* promoter IV and QoL domains in a sample of Brazilian police officers.

2. Materials and methods

2.1. Human subjects

This study was approved by the Ethics Committee on Human Research, Health Sciences Center, Universidade Federal do Espírito Santo, Brazil, under approval number 5382872/2022 (CAAE: 53145521.1.0000.5060). Informed consent was obtained from all individual participants included in the study.

The study population consisted of military police officers from Espírito Santo, Brazil. This study is part of a project entitled "SOMA-SI - Self-Management of Well-Being Programs through Interventions for the Military Police from Espírito Santo."

2.2. Study design

This cross-sectional study was designed to investigate the relationship between the QoL and *BDNF* gene methylation in exon IV among police officers. The methodology included anthropometric measurements, assessment of QoL using the World Health Organization Quality of Life Brief Version questionnaire (WHOQOL-BREF) (THE WHOQOL GROUP, 1998), assessment of depressive symptoms using the Depression, Anxiety, and Stress Scale-21 (DASS-21) (Lovibond and Lovibond, 1995), and a semi-structured questionnaire to assess socioeconomic status and lifestyle factors. Data were collected between April and December 2022. Additionally, blood samples were collected on the same day for molecular and epigenetic analyses.

The inclusion criteria for this study were: adults aged over 18 years, of either sex, who were active-duty military police officers residing in the state of Espírito Santo and who provided written informed consent. Officers were excluded if they were temporarily or permanently on leave from police duties during the study period or presented cognitive impairment that could affect their ability to complete the questionnaires.

2.3. Scales

2.3.1. Quality of life assessment

A variation of the WHOQOL-100 questionnaire was used, specifically, the Brazilian Portuguese version of the WHOQOL-BREF (THE WHOQOL GROUP, 1998; Fleck et al., 2000). This instrument was developed as a shorter and more practical alternative to the original, designed to facilitate easier application while preserving the assessment of key QoL dimensions. The WHOQOL-BREF comprises 24 self-reported items distributed across four domains: physical health, psychological well-being, social relationships, and the environment. The results were presented on a scale ranging from 0 to 100.

Cutoff points were defined according to Cruz et al. (Cruz et al., 2011) because they provided cutoff points specifically for the Brazilian sample. These cutoff points were categorized separately for men and women in each assessed domain (Cruz et al., 2011). In the physical domain, the cutoff point was 61 for both men and women. In the psychological domain, the cutoff points were 67 for men and 63 for women. For the social relationships domain, the cutoff point was 75 for both genders. In the environment domain, the cutoff points were 63 for men and 59 for women.

2.3.2. Depression and stress symptoms assessment

The DASS-21 is a self-assessment questionnaire widely used to measure levels of anxiety, depression, and stress and has been validated in Brazil (Lovibond and Lovibond, 1995; Vignola and Tucci, 2014). The instrument has been used in various clinical contexts (Francis et al., 2019; Hopper et al., 2019; Lopresti et al., 2019) and consists of 21 items, with each of the three areas assessed using seven specific questions. Responses are given on a 4-point scale, ranging from 0 (strongly disagree) to 3 (strongly agree), based on how the individual felt in the last week. The scores for each subscale are added together and then multiplied by 2.

In this study, quantitative scores were used for statistical analyses, while categorical groupings were applied to characterize the sample. For the categorization of depressive and stress symptoms, the scores were classified into the following levels according to symptom intensity: normal, mild, moderate, severe, and extremely severe (Lovibond and Lovibond, 1995). In this study, only the cutoff score from the depression and stress subscales was used, and participants were classified as either Normal or depressive/stress symptoms (mild, moderate, severe, or extremely severe symptoms).

2.3.3. Sociodemographic, physical, and lifestyle assessment

Sociodemographic, physical and lifestyle characteristics were

assessed using a semi-structured questionnaire based on participants' self-report. The variables collected included: age (years); gender (female and male); antidepressant use (yes or no); current alcohol consumption (yes or no); current smoking status (yes or no); self-reported sleep quality (good, moderate, or poor); and physical activity practice of at least 30 min per day (number of days per week).

2.3.4. Anthropometric assessments and conicity index

Body weight was measured primarily using the segmental bioelectrical impedance device InBody 270 (InBodyCo®) and, when necessary, the Tanita B601 (Tanita Corp®) bipolar bioimpedance balance. Both devices were calibrated according to the manufacturer's instructions. Height was measured using a stadiometer (maximum height capacity of 2.10 m and precision of 0.5 cm). Waist circumference (WC) was measured using an inelastic tape measure with an accuracy of 0.1 cm and a maximum length of 2 m.

The conicity index is an anthropometric measure used to assess body fat distribution and has been proposed (Valdez, 1991) as an efficient indicator of visceral fat and cardiovascular risk (Caitano Fontela et al., 2017). To calculate the conicity index, measurements of weight (kg), height (m), and WC (m) were required.

In this study, we chose to use the conicity index because it provides a more accurate assessment by focusing on WC and fat distribution (Caitano Fontela et al., 2017). Body mass index calculations are less accurate in some populations because it does not distinguish between fat mass and body mass (Messner et al., 2024).

2.3.5. DNA extraction and quantitative pyrosequencing methylation assays

DNA was extracted using the Wizard® Genomic DNA Purification Kit (PROMEGA) according to the manufacturer's instructions.

For the methylation analysis, exon IV of the *BDNF* gene was the focus, specifically targeting nine sites (UCSC Genome Browser Human Dec. 2013 [GRCh38/hg38] Assembly - chr11:27,701,519–27,701,826) (Braithwaite et al., 2015). The promoter region of exon IV of the *BDNF* gene, which contains the sequence where the cyclic AMP-responsive element-binding protein (CREB) transcription factor binds (Sabatucci et al., 2020), was examined. The CpG sites corresponding to CpGs 1–9 were analyzed (Fig. 1). The genomic coordinates of these CpG sites were based on regions previously analyzed by Braithwaite et al. (Braithwaite et al., 2015). This region was selected because it has been consistently associated with stress, psychiatric disorders, and cognition through epigenetic modifications (Kundakovic et al., 2015; Moreno et al., 2023; Ferrer et al., 2019; Quaioto et al., 2023; Zheleznyakova et al., 2016; Fungaro Rissatti et al., 2024).

Genomic DNA was treated with bisulfite using the EZ® DNA Methylation Gold Kit (Zymo Research, Irvine, CA, USA) according to the manufacturer's instructions. Methylation analysis of bisulfite treated genomic DNA was performed using the PSQ96ID Pyrosequencer (Qiagen®, Valencia, CA, USA) with PyroMark Gold Q96 reagents (Qiagen®, Valencia, CA) following the manufacturer's protocol. Two sequencing primers were used due to the size of the amplicon. The analyzed primer sequences corresponded to the region studied by Braithwaite et al. (Braithwaite et al., 2015). Detailed information on the analyzed region, PCR primers, conditions, and pyrosequencing primers can be found in Supplementary Table 1.

2.4. Statistical analysis

The Shapiro–Wilk normality test was used to examine normality. Socioeconomic and lifestyle variables were presented as relative and absolute frequencies. Continuous variables were presented as mean and standard deviations or medians and interquartile ranges (IQR).

DNA methylation data exhibited a deviation from normality, as assessed by the Shapiro–Wilk test. Given the continuous distribution of the outcome variables, generalized linear models (GzLM) with a gamma distribution and log link function were employed, an approach widely recommended for this type of data (Nelder and Wedderburn, 1972). Model fit was evaluated using the Akaike Information Criterion (AIC), with lower values indicating better model adequacy.

Multivariate GzLMs with gamma distribution were then used to

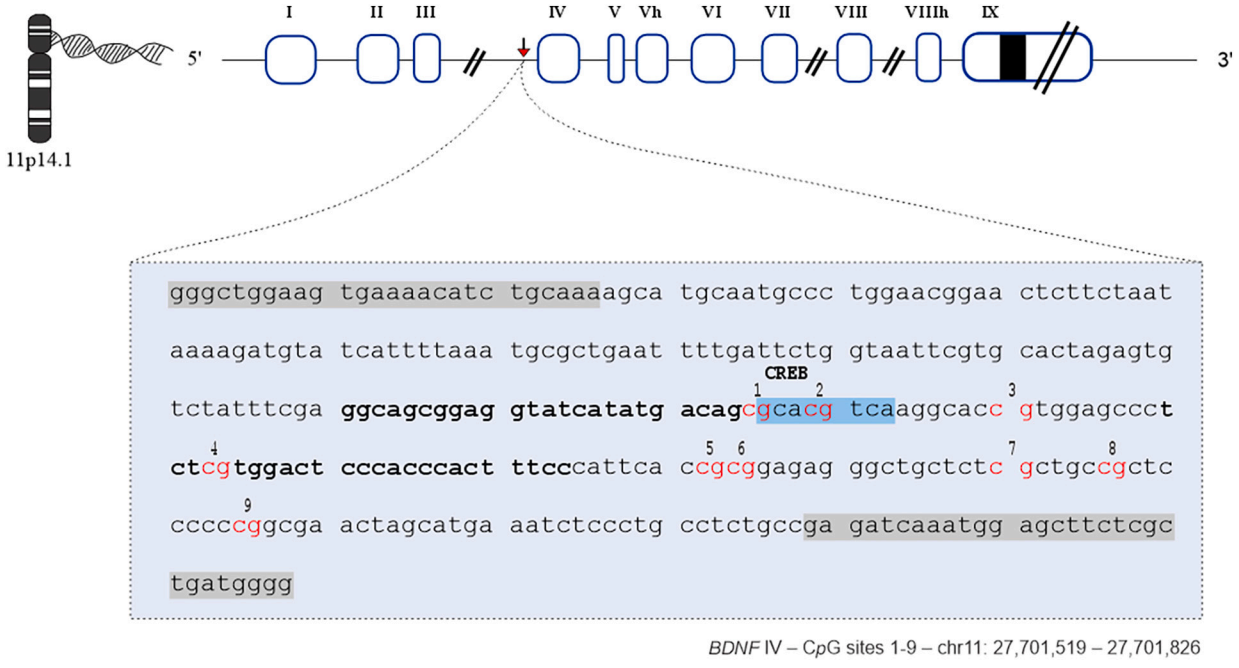

Fig. 1. Region of the *BDNF* gene Exon IV promoter examined in this study (chr11:27,701,519–27,701,826). Genomic coordinates are based on the UCSC Genome Browser Human Assembly (GRCh38/hg38), following the region described by Braithwaite et al. (2015). Exons are represented as boxes, and introns as lines. Roman numerals indicate exon numbers. The red marks and numbers represent the analyzed CpG sites. PCR primers are shaded in gray, sequencing primers are in bold, and the transcription factor (CREB) binding sequence is highlighted in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

investigate the associations between site-specific DNA methylation levels of the *BDNF* gene and QoL domains in police officers. In these models, each *BDNF* CpG site was included as a dependent variable, while the QoL domains (physical, psychological, social relationships, and environment) were treated simultaneously as independent variables. All models were adjusted for potential confounders selected a priori based on biological plausibility and previous literature, including age, conicity index, physical activity level, sleep quality, depressive symptoms, antidepressant use, current smoking status, and current alcohol consumption (Bus et al., 2011a; Bus et al., 2011b).

To account for the potential correlation across the studied CpG sites within *BDNF* exon IV and to address the within-region epigenetic structure, a Spearman's rank correlation matrix was computed for CpG sites 1 through 9. Consistent with the regional epigenetic structure, methylation levels were significantly and positively inter-correlated (Supplementary Table 2), with coefficients ranging from 0.219 to 0.745 (all $p < 0.05$). However, the predominantly moderate magnitude of these correlations suggests a degree of independent variability between sites. Therefore, site-specific analyses were prioritized over aggregate measures to capture nuanced associations with QoL that might otherwise be obscured by a regional mean.

Statistical analyses were performed using SPSS software, version 21.0 (IBM®). A 95% confidence level was applied, and a $p < 0.05$ was considered significant.

3. Results

3.1. Sociodemographic, clinical, lifestyle, physical characteristics, QoL evaluation, and DNA methylation profile

A total of 166 military officers participated in the study. The inter-individual factors, lifestyle factors, physical characteristics, and QoL aspects of this sample are presented in Table 1. Most of the participants were male (77.1%), with ages ranging from 26 to 56 years, and a median age of 38 years (IQR = 14). Symptoms of depression and stress were prevalent in 50.3% and 50% of participants, respectively. *BDNF* methylation values at each CpG site are detailed in Table 2.

Quality of life assessment revealed that most participants reported a worse QoL in the psychological (54.5%), social relationships (58.3%), and environment (62.7%) domains. In contrast, 58.8% of the participants were classified as having a better QoL in the physical domain.

3.2. Relationship between QoL evaluation and BDNF exon IV methylation

To assess the relationship between QoL domains and *BDNF* exon IV promoter region methylation, we performed GzLM. In the models, each site-specific *BDNF* CpG was added as a dependent variable, and QoL domains (physical, psychological, social relationships, and environment) were included as independent variable. Confounding factors were age, conicity index, depression symptoms, antidepressant use, current smoking, current alcohol consumption, physical activity, and self-reported sleep quality.

Analysis of the relationship between the QoL domains and the methylation of the *BDNF* exon IV promoter region showed that CpG site 3 ($\beta = -0.358$, $p = 0.026$), 4 ($\beta = -0.264$, $p = 0.035$), 7 ($\beta = -0.333$, $p = 0.022$), and 8 ($\beta = -0.240$, $p = 0.024$) were associated with the psychological domain. Regarding the psychological domain of QoL, a consistent pattern was observed where individuals with "Better QoL" exhibited lower DNA methylation levels compared to those with "Worse QoL". These results indicated an inverse relationship, in which lower methylation was associated with a better quality of life. Other specific CpG sites were not associated with QoL domains in this study (Table 3).

4. Discussion

In this study, we investigated the association between DNA methylation levels at specific CpG sites within the *BDNF* exon IV promoter and quality of life (QoL) domains in Brazilian police officers, a population chronically exposed to occupational stress. QoL is influenced by several factors, such as socioeconomic status (Bdier et al., 2023), lifestyle (da Costa et al., 2020), stress (Kumar et al., 2018), and health conditions (Bdier et al., 2023; Zare et al., 2020). These factors interact in a complex manner, exerting environmental pressure that may correspond to adaptive changes in the epigenome of several genes, including *BDNF* (Treble-Barna et al., 2023). Epigenetic modifications can alter gene expression and influence mental health, potentially fixing phenotypes that, despite being adaptive, may manifest as diseases. However,

Table 1
Characterization of all participants.

Characteristics	All
Socio-demographic	
Age, *median (IQR)*	38 (14)
Gender, *n (%)*	
Female	38 (22.9)
Male	128 (77.1)
Clinical, Physical and Lifestyle Characteristics	
Psychological health	
Conicity index, *median (IQR)*	1.2 (0.94)
Not Evaluated#	2
Depression (DASS-21), *n (%)*	
Normal	71 (49.7)
Depressive symptoms	72 (50.3)
Depression score, *median (IQR)*	10 (18)
Not Evaluated#	23
Stress (DASS-21), *n (%)*	
Normal	71 (50.0)
Stress symptoms	71 (50.0)
Stress score, *median (IQR)*	15 (14)
Not Evaluated#	24
Antidepressant use, *n (%)*	
Yes	24 (16.7)
No	120 (83.3)
Not Evaluated#	22
Current Alcohol, *n (%)*	
Non-alcohol	72 (43.4)
Alcohol	94 (56.6)
Current Smoking, *n (%)*	
Non-smoker	150 (90.9)
Smoker	15 (9.1)
Not Evaluated#	1
Self-reported sleep quality, *n (%)*	
Good	39 (23.6)
Moderate	56 (33.9)
Poor	70 (42.4)
Not Evaluated#	1
Physical activity	
Physical activity (days a week), *median (IQR)*	2 (3)
WHOQOL-BREF Domains	
Physical, *n (%)*	
Worse	68 (41.5)
Better	96 (58.8)
Physical Score, *median (IQR)*	67.8 (25)
Not Evaluated#	2
Psychological, *n (%)*	
Worse	90 (54.5)
Better	75 (45.5)
Psychological Score, *median (IQR)*	62.5 (23.9)
Not Evaluated#	1
Social relationships, *n (%)*	
Worse	95 (58.3)
Better	68 (41.7)
Social Score, *median (IQR)*	66.7 (25)
Not Evaluated#	3
Environment, *n (%)*	
Worse	101 (62.7)
Better	60 (37.3)
Environment Score, *median (IQR)*	56.2 (21.1)
Not Evaluated#	5

IQR: Interquartile range; #Not available: number of participants not available (not considered in the statistical calculations).

Table 2
BDNF methylation sites.

BDNF IV – CpG sites 1–9 - chr11:27,701,519–27,701,826*	Median (IQR)
BDNF - CpG 1 (%)	3.23 (1.79)
BDNF - CpG 2 (%)	1.66 (2.51)
BDNF - CpG 3 (%)	1.82 (3.08)
BDNF - CpG 4 (%)	2.00 (2.98)
BDNF - CpG 5 (%)	2.87 (5.14)
BDNF - CpG 6 (%)	1.04 (1.96)
BDNF - CpG 7 (%)	2.32 (3.14)
BDNF - CpG 8 (%)	1.77 (2.39)
BDNF - CpG 9 (%)	2.31 (1.25)

the relationship between epigenetic modifications of the *BDNF* gene and QoL remains poorly understood, particularly in populations exposed to high stress levels, such as police officers.

The association between psychological QoL and *BDNF* methylation was not uniform across the exon IV region. Specifically, CpG sites 3, 4, 7, and 8 showed significant inverse associations, even after adjustment for sociodemographic, lifestyle, anthropometric, and stress-related covariates. No consistent associations were observed for the physical, social, or environmental QoL domains, suggesting a domain-specific relationship between *BDNF* epigenetic regulation and psychological well-being and these specific coordinates within the promoter IV are more sensitive to the psychological state of police officers than flanking sites.

This region is relevant due to its proximity to the binding site of CREB transcription factor (Fig. 1). Interestingly, while the core CREB binding motif is primarily located near CpGs 1 and 2 (Braithwaite et al., 2015; Kundakovic et al., 2015), our findings revealed significant associations only at adjacent downstream sites (CpGs 3, 4, 7, and 8). This specific pattern highlights the heterogeneous nature of DNA methylation across the promoter region, suggesting that the epigenetic correlate of occupational stress in this study is localized to specific regulatory coordinates rather than uniformly affecting the entire CREB binding area. However, elucidating the precise mechanistic impact of this localized pattern will require further functional investigation.

Our findings are consistent with those of Ferrer et al. (Ferrer et al., 2019), who evaluated increased *BDNF* methylation and decreased gene expression associated with the development of depressive symptoms, leading to worsening of QoL. Increased methylation has also been associated with early life adversity (Kundakovic et al., 2015) and conditions such as Alzheimer's disease (Amidfar et al., 2020) and depression (Penner-Goeke and Binder, 2019). Li et al. (Li et al., 2021) identified significantly higher methylation levels at two CpG sites in exon VI of *BDNF* in patients with major depressive disorder than those in healthy individuals. These authors suggest that *BDNF* methylation in exon VI may serve as an epigenetic marker of depression.

Additionally, Na et al. (Na et al., 2016) observed a correlation between *BDNF* methylation and reduced cortical thickness in patients with major depressive disorder, indicating a possible link between *BDNF* methylation and brain alterations. However, DNA methylation is highly tissue-specific, and epigenetic patterns can vary between blood and brain regions.

Conversely, the literature suggests that a decrease in *BDNF* methylation may be associated with enhanced gene expression, potentially reflecting increased serum BDNF levels (Fachim et al., 2022; Zwolińska et al., 2024). Studies have shown that higher BDNF levels are associated with better cognitive (Costa et al., 2015) and psychiatric states (Polyakova et al., 2015). Thus, decreased methylation of *BDNF* gene exon IV may be linked to a better QoL.

BDNF gene expression can be modulated by environmental factors, particularly chronic stress (Bennett and Lagopoulos, 2014). Police officers frequently encounter stressful situations involving danger, risks to life, violence, and criminal activities. Prolonged exposure to chronic stressors may act as an environmental pressure associated with epigenetic variations, which correlate with adaptive effects on physical and

Table 3
GzLM results for models with each CpG, were adjusted by confounding factors: self-reported sleep quality, age, conicity index, depression symptoms, physical activity, antidepressant use, current smoking, and current alcohol consumption.

BDNF CpG sites	WHOQOL-BREF Domain	Parameter Estimates				
		β	Std. Error	95% CI	Wald x^2	*p*-value
1	Physical	0.010	0.0859	−0.158 – 0.178	0.013	0.908
	Psychological	−0.51	0.0777	−0.204 – 0.101	0.437	0.509
	Social Relationships	0.013	0.0859	−0.155 – 0.182	0.024	0.878
	Environment	−0.066	0.0825	−0.227 – 0.096	0.630	0.427
2	Physical	−0.039	0.1395	−0.312 – 0.235	0.078	0.780
	Psychological	−0.042	0.1326	−0.302 – 0.218	0.100	0.752
	Social Relationships	0.011	0.1325	−0.248 – 0.271	0.007	0.932
	Environment	0.037	0.1304	−0.219 – 0.292	0.080	0.778
3	Physical	0.043	0.1937	−0.337 – 0.423	0.050	0.824
	Psychological	−0.358	0.1613	−0.674 – −0.042	4.927	**0.026**
	Social Relationships	−0.199	0.2056	−0.602 – 0.204	0.938	0.333
	Environment	−0.027	0.1733	−0.367 – 0.312	0.025	0.875
4	Physical	0.48	0.1530	−0.252 – 0.347	0.097	0.755
	Psychological	−0.264	0.1255	−0.510 – −0.018	4.429	**0.035**
	Social Relationships	−0.176	0.1470	−0.464 – 0.112	1.432	0.231
	Environment	−0.027	0.1353	−0.292 – 0.239	0.38	0.845
5	Physical	0.150	0.1940	−0.230 – 0.530	0.599	0.439
	Psychological	−0.258	0.1672	−0.585 – 0.070	2.375	0.123
	Social Relationships	−0.039	0.1861	−0.404 – 0.325	0.045	0.833
	Environment	−0.347	0.1790	−0.698 – 0.004	3.755	0.053
6	Physical	0.169	0.1556	−0.136 – 0.474	1.184	0.277
	Psychological	−0.244	0.1379	−0.514 – 0.026	3.125	0.077
	Social Relationships	−0.161	0.1449	−0.445 – 0.123	1.239	0.266
	Environment	−0.084	0.1356	−0.349 – 0.182	0.382	0.537
7	Physical	−0.152	0.1807	−0.506 – 0.203	0.704	0.401
	Psychological	−0.333	0.1456	−0.619 – −0.048	5.241	**0.022**
	Social Relationships	0.083	0.1771	−0.264 – 0.430	0.219	0.640
	Environment	−0.152	0.1720	−0.489 – 0.185	0.780	0.377
8	Physical	−0.189	0.1262	−0.436 – 0.058	2.246	0.134

(*continued on next page*)

Table 3 (*continued*)

BDNF CpG sites	WHOQOL-BREF Domain	Parameter Estimates				
		β	Std. Error	95% CI	Wald x^2	*p*-value
9	Psychological	−0.240	0.1065	−0.448 – −0.031	5.061	**0.024**
	Social Relationships	0.020	0.1198	−0.215 – 0.255	0.028	0.866
	Environment	0.018	0.1239	−0.224 – 0.261	0.022	0.882
	Physical	0.024	0.1098	−0.191 – 0.239	0.048	0.826
	Psychological	−0.168	0.1066	−0.377 – 0.041	2.479	0.115
	Social Relationships	0.002	0.1021	−0.198 – 0.202	<0.001	0.986
	Environment	0.003	0.0998	−0.193 – 0.198	0.001	0.978
mean (CpG 1–9)	Physical	−0.026	0.1599	−0.287 – 0.339	0.027	0.870
	Psychological	−0.247	0.1379	−0.517 – 0.024	3.202	0.074
	Social Relationships	0.103	0.1575	−0.206 – 0.412	0.429	0.513
	Environment	−0.211	0.1516	−0.508 – 0.087	1.929	0.165

GzLM: Generalized linear models obtained with Gamma distribution.

psychological health (Leino et al., 2011).

QoL is closely related to physical and mental well-being. Public safety professionals, such as police officers, require adequate attention because of work-related stress and demanding labor (da Costa et al., 2020; Tavares et al., 2021). The stressful nature of police work can negatively affect their QoL and, in some cases, affect their mental and physical health (Wu et al., 2019; Minayo et al., 2011).

There is a close relationship between BDNF and the hypothalamus–pituitary–adrenal (HPA) axis, which regulates stress responses (Suri and Vaidya, 2013; Miao et al., 2020). Chronic stress can have a significant epigenetic effect on HPA axis-related genes, reducing BDNF levels, particularly in the hippocampus, and causing an imbalance in stress responsiveness (Duman and Monteggia, 2006). This altered adaptive condition is linked to impaired ability to cope with stress and decrease stress resilience, and is associated with a high allostatic load and a decline in the QoL among police officers.

To contextualize our findings within the broader literature on stress-related phenotypes, it is well established that higher *BDNF* promoter methylation is frequently associated with adverse psychiatric conditions, such as depression, and early-life trauma (Kundakovic et al., 2015; Penner-Goeke and Binder, 2019; Li et al., 2021). Conversely, our study demonstrates that lower methylation at specific CpG sites (3, 4, 7, and 8) is linked to better psychological QoL scores. Instead, maintaining lower methylation at these specific promoter sites may be a distinguishing feature of active police officers that sustain their quality of life despite high environmental demands.

Some limitations of this study should be considered. First, DNA methylation was assessed in peripheral blood. Although *BDNF* exon IV promoter methylation is frequently studied as a biomarker in neuropsychiatric and stress-related contexts, previous studies suggest partial concordance between blood and brain methylation in regulatory regions of stress-related genes (Ikegame et al., 2013; Kundakovic et al., 2015). Consequently, peripheral measures cannot be directly extrapolated to central nervous system processes. Second, we did not assess *BDNF* gene expression or circulating protein levels, therefore, functional inferences regarding the biological consequences of the observed methylation patterns remain indirect.

Third, while our sample of 166 participants provides adequate statistical power to detect the moderate epigenetic associations observed in our multivariate models, larger samples are necessary to identify more subtle effect sizes. Consequently, caution is needed when generalizing these results, as our conclusions cannot be directly extrapolated to the broader population. Fourth, the cross-sectional design of this study precludes causal inference and does not allow determination of the temporal directionality between quality of life and *BDNF* methylation. Finally, despite rigorous adjustment for multiple confounders, residual confounding related to unmeasured occupational or psychosocial stressors, such as shift work, night duty, cumulative years of service, and specific trauma exposure, cannot be ruled out.

Despite these limitations, this study contributes to the growing evidence linking epigenetic regulation of stress-related genes to psychological well-being. By focusing on a high-risk occupational group and identifying site-specific associations within a key regulatory region of the *BDNF* gene, our findings highlight the potential relevance of epigenetic markers in understanding individual differences in psychological quality of life under chronic stress exposure. To our knowledge, this is the first study to investigate the association between *BDNF* gene methylation and QoL. Future longitudinal studies integrating epigenetic, transcriptomic, and proteomic measures of BDNF are warranted to clarify the temporal dynamics and biological mechanisms underlying the relationship between quality of life and *BDNF* gene regulation and elucidate the directionality between health, *BDNF* gene methylation, and QoL.

5. Conclusion

In conclusion, this study demonstrates a site-specific association between *BDNF* gene methylation and the psychological Quality of Life (QoL) domain in police officers. Our results indicate that individuals exposed to similar environmental pressures, such as high-stress police work, exhibit heterogeneous methylation profiles. Overall, these findings contribute to a better understanding of the association between epigenetic modifications and psychological health in high-risk occupational groups.

CRediT authorship contribution statement

Ivana Alece Arantes Moreno: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Aline Ribeiro Borçoi:** Writing – review & editing, Investigation, Funding acquisition, Formal analysis. **Suzanny Oliveira Mendes:** Formal analysis, Data curation. **Pierre Augusto Victor da Silva:** Writing – review & editing, Formal analysis, Data curation. **Flavia Imbroisi Valle Errera:** Writing – review & editing. **Carmem Luiza Sartório:** Writing – review & editing, Data curation, Conceptualization. **Carlos Henrique Pagani Corrêa:** Investigation, Data curation. **Flávia Vitorino Freitas:** Writing – review & editing, Formal analysis. **Sonia Alves Gouvea:** Investigation. **José Claudio Casali-da-Rocha:** Writing – review & editing. **Aurelio dos Santos Couto:** Data curation. **Amanda Sgrancio Olinda:** Investigation. **Ester Ribeiro Cunha:** Investigation. **Bárbara Risse Quaioto:** Investigation. **Marcele Lorentz Mattos de Souza:** Investigation. **Tamires dos Santos Vieira:** Investigation, Data curation. **Joaquim Gasparini:** Writing – review & editing, Formal analysis. **Bruna Pereira Sorroche:** Investigation. **Lidia Maria Rebolho Batista Arantes:** Investigation. **Elizeu Batista Borloti:** Investigation, Conceptualization. **Pedro Luiz Ferro:** Project administration. **Adriana Madeira Álvares-da-Silva:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genrep.2026.102478.

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