ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

Val66Met and Genetic Predisposition to Obesity, Mood, and Sleep Disorders

Shivangi Sharma[1]

[1]Independent Researcher
Ludhiana, Punjab

Publication Date: 2025/07/16

Abstract: Brain-derived Neurotrophic Factor (BDNF) has several polymorphisms, one of the most recognized being the Val66Met polymorphism, which is associated with a range of disorders. This review examines current evidence on Val66Met polymorphism, highlighting how Met allele carriers tend to gain weight, exhibit heightened emotional sensitivity, and experience poor sleep quality. The Met allele consistently emerged as a contributor to disrupted neuroplasticity, impaired emotional regulation, and altered metabolic function. Some strategies, such as lifestyle and nutrition-based interventions, showed positive results in increasing BDNF levels, potentially helping to mitigate these effects. The consequences of Val66Met polymorphism might be aggravated by lifestyle factors such as stress, poor diet, and lack of physical activity. Greater insight into the role of Val66Met may help create more tailored and efficient ways of maintaining physical and mental health.

Keywords: *BDNF, Metabolism, Mood, Obesity, Sleep, Val66Met Polymorphism.*

How to Cite: Shivangi Sharma (2025) Val66Met and Genetic Predisposition to Obesity, Mood, and Sleep Disorders. *International Journal of Innovative Science and Research Technology*, 10(7), 902-913.
https://doi.org/10.38124/ijisrt/25jul511

I. INTRODUCTION

The Brain-Derived Neurotrophic Factor (BDNF) is a key protein that supports neural growth, survival, and synaptic plasticity (Vidović et al., 2020). The BDNF gene, located on chromosome 11, contains a common single nucleotide polymorphism (SNP), in which a valine to methionine substitution (Val66Met – SNP, rs6265) is associated with altered BDNF expression and activity (Devlin et al., 2021). The BDNF Val66Met polymorphism has been linked to various physiological and psychological conditions, with studies suggesting that Met carriers may be more vulnerable to obesity, due to disruptions in energy balance and appetite regulation (Bonaccorso et al., 2015). Additionally, this SNP appears to influence sleep architecture, with research showing disrupted sleep patterns among Met carriers (Saitoh et al., 2018). The Val66Met also plays a role in mood-related disorders, such as depression and anxiety, possibly by affecting stress reactivity and emotional regulation (Devlin et al., 2021). It interferes with activity-dependent BDNF release, thereby influencing learning, memory, and synaptic function (K. S. Park et al., 2020). This review brings together recent research on how BDNF Val66Met polymorphism may increase risk of obesity, mood disorders, and sleep disturbances and how these conditions also overlap and share common biological pathways. It also focuses on identifying holistic strategies that support more personalized treatments.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

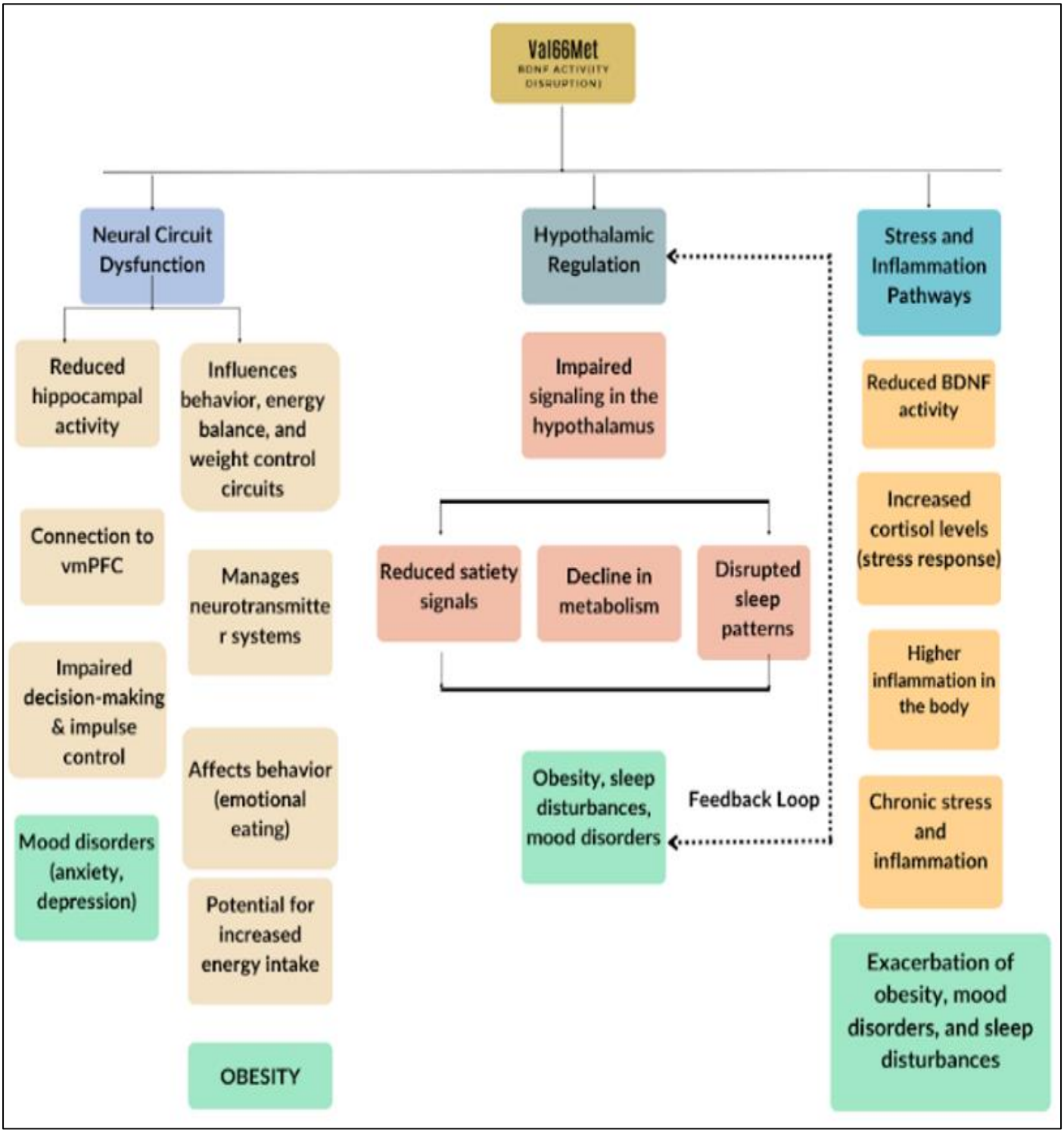

Fig 1 Interconnected Influence of Val66Met Polymorphism on Obesity, Sleep, and Mood (Created by Author)

II. IMPACT OF VAL66MET SNP ON OBESITY

BDNF helps regulate appetite, energy use, and metabolism (De Assis et al., 2021). When the Val66Met is present, it affects how BDNF is processed in the cells, making the conversion of proBDNF into its active form difficult (C. Park et al., 2017). As a result, Met allele carriers have less mature BDNF compared to non-carriers, which may influence metabolic function and contribute to obesity (De Assis et al., 2021).

- *Energy Imbalance and Metabolic Risk:*

When BDNF activity declines, body becomes less efficient in using energy during both active and resting states, as a result excess nutrients are more likely to be stored as fat and thereby promote weight gain (Rana et al., 2021). Additionally, in Met allele carriers, dysfunctional BDNF signaling, disrupts fat storage and blood sugar control, increasing the risk of insulin resistance and type 2 diabetes. Reduced BDNF levels also increase triglycerides and low-density lipoprotein (LDL) levels, contributing to greater cardiovascular disease risk (Honarmand et al., 2021).

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

- *Hypothalamic Dysregulation:*

The hypothalamus helps regulate appetite and BDNF manages its signals of hunger and fullness. Reduced levels of BDNF due to Met allele impairs hypothalamic mechanisms that mediate satiety signals. As a result, appetite control weakens, metabolism slows down and sleep is disturbed, eventually leading to overeating (Goldfield et al., 2021). Additionally, diminished BDNF activity contributes to a preferential selection of high calorie foods, increasing the risk of obesity (Goldfield et al., 2021).

- *Impaired Stress and Inflammatory Response:*

The Val66Met SNP modulates BDNF activity, affecting the body's response to stress and inflammation. The role of BDNF is to buffer the stress reaction and inflammation initiated in the body. In the presence of Met allele, the activity of BDNF is tapered down and the brain is not able to adapt to stress. Compromised activity of BDNF results in enhanced activity of cortisol and accelerates the rate of inflammation (Dooley et al., 2016).

- *Multifactorial Nature of Obesity:*

Obesity is a multifaceted disorder influenced by numerous factors which can be broadly categorized under genes and environment (M. Zhang et al., 2024). Polymorphisms like Val66Met are accompanied with an amplified rate of inflammation that impairs metabolic function resulting in obesity (Amadio et al., 2022). But the diverse nature of obesity is evident in the fact that apart from Val66Met SNP, there are many other variations that could bring out the expression of the disease. Nevertheless, factors such as nutrition, physical activity, socioeconomic status have a significant role to play in the expression of obesity symptoms (M. Zhang et al., 2024).

III. IMPACT OF VAL66MET SNP ON SLEEP ARCHITECTURE AND QUALITY

Sleep architecture refers to the normal structure or pattern of sleep cycle of an individual which is influenced by physiological, psychological, genetics, lifestyle, and environmental factors (Desai et al., 2024). The Val66Met SNP significantly affects the sleep architecture, duration, and quality which consequently may alter sleep consolidation. Met allele carriers tend to have greater sleep fragmentation and disrupted circadian rhythms. These disturbances indicate a genetic origin for variability in sleep homeostasis and stability (Zaki et al., 2019). This connection is imperative to investigate genetic effects on sleep regulation.

- *Sleep Disruption and Circadian Instability:*

The hypothalamus contains suprachiasmatic nucleus (SCN), the body's master clock, which regulates circadian rhythms and coordinates the sleep-wake cycle. Both BDNF and its receptor - Tropomyosin receptor kinase B (TrkB) are highly expressed in the SCN, supporting the idea that BDNF's influence on sleep is more biologically driven rather than socially conditioned. Disrupted BDNF signaling from Val66Met may result in altered sleep duration, instability, and changes in sleep structure. Met allele carriers also show variations in bed time, further confirming BDNF's involvement in circadian regulation association with sleep. Lower BDNF levels have been linked to sleep disorders as well as heightened vulnerability to circadian rhythm sleep disorders (CRSDs), underlining its key role in sleep homeostasis (Saitoh et al., 2018).

- *Sleep Inefficiency and Neurocognitive Risk:*

Individuals with Met allele often struggle to maintain continuous sleep, leading to increased sleep fragmentation and poor sleep retention. These disturbances can interfere with homeostatic regulation of sleep, ultimately reducing overall sleep efficiency and consistency (Gosselin et al., 2016). One key component of restorative sleep is Non-Rapid Eye Movement (NREM) sleep, particularly its slow-wave activity (SWA), which is essential for deep, restorative rest and cognitive recovery. SWA supports memory consolidation, synaptic homeostasis, and overall brain repair. Within NREM sleep, slow-wave sleep (SWS) represents deepest stage and is characterized by high-amplitude, low-frequency brain waves. This stage is critical for neuroplasticity, metabolic waste clearance, and cognitive resilience, all of which help maintain optimal brain function (Mayeli et al., 2024). While Val66Met polymorphism does not directly impact SWA or SWS, it may weaken sleep's ability to support cognitive recovery and alertness upon waking. As a result, Met allele carriers often show altered sleep-wake patterns, potentially impacting circadian rhythm stability and cognitive benefits typically gained from sleep. This diminished restorative function can lead to variations in alertness, learning capacity and memory consolidation (Gosselin et al., 2016).

Notably, disruptions in SWS, have been associated to cognitive deficits, including reduced memory retention and increased risk of neurodegenerative disorders such as Alzheimer's disease (Muto et al., 2021).

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

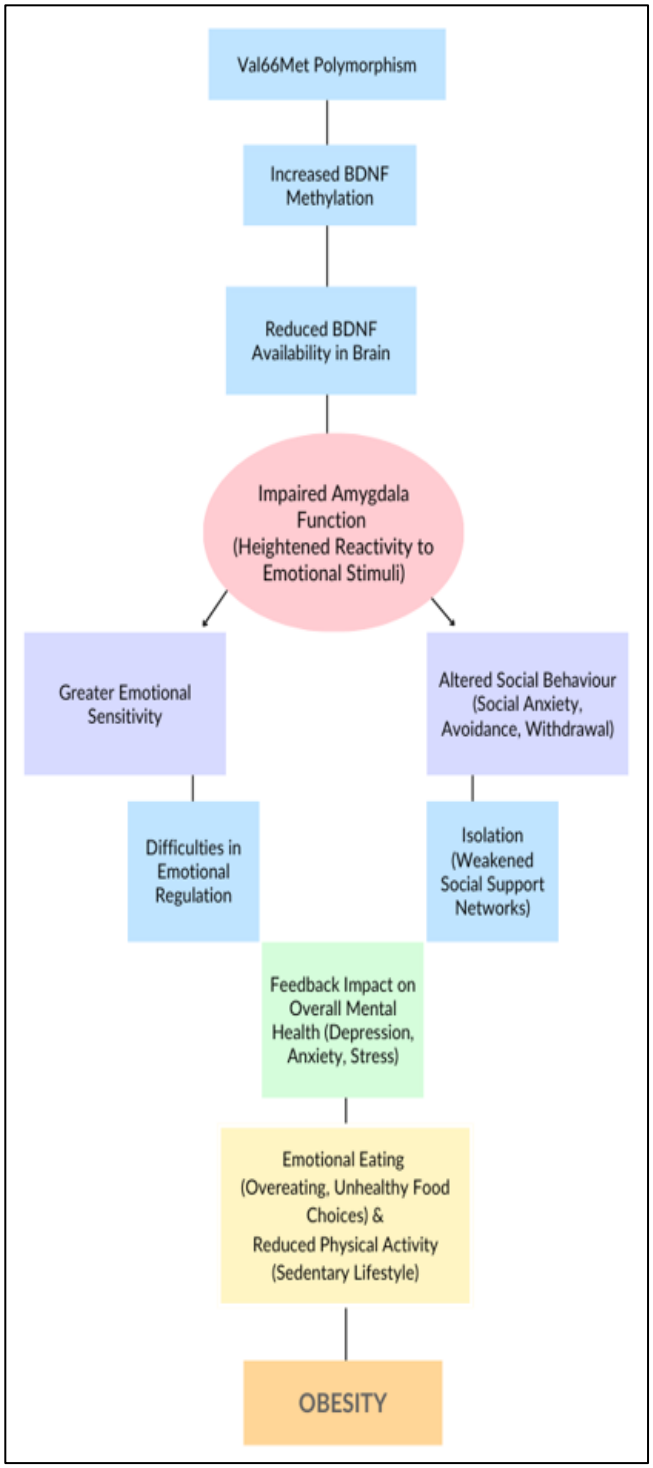

Fig 2 Impact of Val66Met Polymorphism on Amygdala Function and Emotional Sensitivity in Obesity (Created by Author)

IV. IMPACT OF VAL66MET SNP ON MOOD AND EMOTIONAL HEALTH

While emotions are immediate reactions to stimuli (Niles et al., 2018), mood is a more sustained affective state influenced by neural circuits and biochemical processes (Shi et al., 2020). The brain's ability to regulate them depends on neurotransmitters and neurotrophic factors. Any disruptions in these mechanisms can lead to mood instability and increase susceptibility to mental health disorders.

- *Reduced Mood Resilience and Emotional Dysregulation:*

Mood resilience refers to an individual's capacity to maintain emotional stability and adapt effectively to stress (Taren et al., 2015). BDNF is responsible for regulating mood resilience. In individuals with Met allele, the expression of BDNF is weakened, and brain function in regulating reaction to stress and emotional stability appears to be compromised (Peters et al., 2021). Reduced levels of BDNF impair neuroplasticity, which is essential for adapting to emotional challenges and maintaining emotional stability, in consequence, this impairment can lead to emotional dysregulation, making individuals more susceptible to mood disorders (Youssef et al., 2018).

- *Amygdala Dysregulation and Emotional Reactivity:*

The amygdala is centrally integrated into the processing of fear, threat, and other negative emotional judgements and is able to form new and store emotionally charged memories (West et al., 2021). Emotional disturbances from negative experiences stem from an overactive amygdala. Due to hyperactivity in the left amygdala there is an increased perception of negativity as compared to positivity which may induce chronic emotional stress over time (Puccetti et al., 2021). The Val66Met polymorphism reduces the expression and discharge of BDNF, critical for healthy function of amygdala. Increased methylation leads to attenuation of the expression of BDNF in the Met allele carriers. Due to the decreased expression of BDNF, reactions to emotions are heightened, and susceptibility to mood disorders associated with depression and anxiety are observed (Redlich et al., 2020). Low concentrations of BDNF impair the activity of the amygdala in controlling emotional responses, and subsequently, intensify feelings and make emotion control difficult (Fungaro Rissatti et al., 2024).

- *Social Emotional Vulnerability:*

The Val66Met polymorphism affects social cognition and social behavior. Altered function in the amygdala affects processing of social information and reactivity to social danger. Greater reactivity in the amygdala will make individuals perceive themselves at heightened vulnerability for criticism, and social rejection. Increased sensitization may manifest in social anxiety, social avoidance, and an inability to form and maintain healthy, meaningful relationships. In extreme cases, one will become hyper-vigilant, isolating and shunning new experiences and sensations which may further reduce mental well-being (Rappaport & Barch, 2020).

- *Unhealthy Behavioral Consequences:*

BDNF plays a significant role in emotional resilience, stress response, and social interactions (Schmitt et al., 2016). Met allele reduces mature BDNF levels, affecting amygdala, leading to emotional sensitivity, poor social cue recognition, emotional eating and reduced motivation for physical activity (Wheeler et al., 2018). These effects reinforce one another where emotional distress worsen lifestyle choices and health (Mahindru et al., 2023). Stress-related hormonal imbalances further contribute to this cycle. Chronic stress elevates cortisol and ghrelin driving cravings for unhealthy foods (Lis et al., 2024) and promoting unhealthy response of emotional eating (Dakanalis et al., 2023), especially in adolescents

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

(Pietrabissa et al., 2021), Depression and anxiety further through low motivation and fear of judgment (McCartan et al., 2020), lead to sedentary habits (Denche-Zamorano et al., 2022). When combined with emotional eating, this results in long term weight gain (Konttinen, 2020). Ultimately, BDNF's central role in emotional instability leads to maladaptive behaviors (Zhao et al., 2018).

➢ *Neural Dysfunction and Cognitive Impairment:*

The Val66Met SNP is linked to reduced connectivity and function in the hippocampus. Met allele carriers have less hippocampus activity, during memory tasks, suggesting impaired capacity to form and sustain neural connections (Xiong et al., 2024). The disruption can affect other cognitive functions, like decision-making and impulsivity, because the hippocampus is interconnected with ventromedial prefrontal cortex (vmPFC), a brain region that is responsible for regulating these behaviors (Hiser & Koenigs, 2018). Additionally, since BDNF is responsible for regulating neurotransmitters like dopamine, norepinephrine, and serotonin, Val66Met may influence reward sensitivity and disrupt associated neural circuits (Martínez-Ezquerro et al., 2017).

V. STRATEGIES TO ENHANCE BDNF LEVELS

➢ *Aerobic Exercises:*

Both acute and chronic exercise have been shown to increase BDNF levels (Kambestad et al., 2023). The intensity of the exercise is also important to consider. Higher-intensity aerobic exercise induce more significant BDNF rise as compared to lower intensity exercises, suggesting that vigorous activity causes more positive changes in BDNF concentration (Jeon & Ha, 2017).

➢ *Sleep:*

Sleep disturbances, such as insomnia, are closely associated with low amounts of BDNF (Furihata et al., 2020). Additionally, decreased sleep duration is associated with lower BDNF levels (Fan et al., 2019). Inadequate rest disrupts BDNF release, impairing cognitive function and increasing vulnerability to mood disorders. Consistent, healthy, undisturbed sleep is crucial for stable and constant synthesis of BDNF, which supports optimal brain function and emotional regulation (Monteiro et al., 2017).

➢ *Antidepressants:*

Antidepressants enhance the expression and activity of BDNF through various epigenetic changes. DNA methylation at BDNF gene regions is related to depression and can decrease neuronal plasticity. These effects might be mitigated through antidepressants by altering epigenetic processes including histone modification (X. Zhang et al., 2023). Although they should only be consumed through the prescription of a physician.

➢ *Omega-3 fatty acids:*

Omega-3 fatty acids are involved in various neuroprotective actions, including improving endothelial dysfunction and counteracting oxidative stress, which could indirectly boost BDNF (Godos et al., 2024). Furthermore, omega-3 fatty acids may modulate BDNF synthesis by interacting with transcription factors or signaling pathways involved in BDNF synthesis (Agh et al., n.d.). Omega-3 supplementation can significantly elevate BDNF levels, supporting neuroplasticity, neurogenesis, and cognitive function. Rich dietary sources of omega-3s include fatty fish (salmon, mackerel, sardines), oysters, meat, eggs, dairy, cereals, nuts, seeds, and certain oils (Patted et al., 2024).

➢ *Zinc:*

In neurons, zinc acts as an enzymatic cofactor and binds to neurotransmitters, influencing brain activity. Rich dietary sources of zinc include meat, shellfish, seeds, nuts, whole grains, millets, sesame and pumpkin seeds, soybeans, chickpeas, and leafy vegetables (Maares & Haase, 2020). Zinc supplementation has been shown to significantly increase serum BDNF levels (De Vargas et al., 2023; Jafari et al., 2020). And zinc might impact molecular pathways involved in BDNF production. By supporting enzymatic activity and neurotransmitter function, zinc contributes to brain health and may enhance BDNF synthesis. Higher BDNF levels have been linked to reduced symptoms of depression, indicating a potential positive impact of zinc on mental health (Solati et al., 2015).

➢ *Polyphenols:*

Polyphenols that are plant-based compounds known for their antioxidant properties are commonly found in foods such as coffee, tea, red wine, citrus fruits, apples, pears, and chocolate (Edmands et al., 2015). These compounds have been shown to have a positive effect on BDNF levels (Pontifex et al., 2021). Especially when combined with exercise or when there is an exposure to environmental stressors like ozone, polyphenols seem to boost BDNF (Morton et al., 2024). So, this suggests that polyphenols not only support BDNF synthesis but also provide additional neuroprotection in adverse environments.

➢ *Folic Acid and Methylcobalamin:*

Folic acid and methylcobalamin both play important roles in brain function and development through supplying substrates for methylation processes in cells. These methylation mechanisms are essential for regulating BDNF expression, which is vital for neuronal survival, growth, and synaptic plasticity. Supplementation with folic acid and methylcobalamin has been shown to elevate serum BDNF levels, enhancing their neurotrophic effects. These vitamins also contribute to neuroprotection by modulating the balance between neurotoxicity and neurotropism in the central nervous system, highlighting their role in maintaining neurotrophic homeostasis (Kasir et al., 2023). Dietary sources of folic acid include leafy green vegetables, fruits, legumes, eggs, seafood, meat, poultry, dairy, and fortified grains (Ledowsky et al., 2022). Vitamin B12 is primarily found in animal-based food sources, including meat, milk, eggs, fish, and shellfish (Al Zoubi et al., 2024).

➢ *Vitamin D:*

Higher Vitamin D levels are associated with increased serum BDNF concentration (Quialheiro et al., 2022). The

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

presence of 1,25-dihydroxyvitamin D3-1-hydroxylase in the central nervous system suggests a direct role for vitamin D in brain function. Active vitamin D supports the synthesis and release of neurotrophic factors, including BDNF, and also contributes to serotonin production by upregulating genes involved in its synthesis. Elevated serotonin levels may further promote BDNF expression and secretion. Vitamin D3 has been shown to increase BDNF concentrations and enhance acetylcholinesterase activity in the brain, likely through modulation of BDNF gene expression. Additionally, the interaction between vitamin D and serum BDNF may underlie its antidepressant effects, suggesting that vitamin D supplementation could reduce depressive symptoms by elevating BDNF levels (Dawoud et al., 2023). It is found in foods such as fatty fish, eggs, liver, lean meats, and low-fat dairy products (Dominguez et al., 2021).

VI. METHODOLOGY

A systematic search of the scientific literature was carried out in an effort to examine the association of BDNF Val66Met polymorphism with its influence on obesity, mood, and sleep. A thorough review of literature from 2015 to 2025 was conducted across PubMed and Scopus, focusing on studies examining how the Met allele of the BDNF Val66Met polymorphism contributes to increased vulnerability to obesity, mood disturbances, and sleep disruption through shared biological pathways such as inflammation, hormonal imbalance, and impaired neural signaling. The search strategy used an array of keywords and MeSH terms including "BDNF," "Val66Met polymorphism," "obesity," "metabolism," "mood," and "sleep."

Articles were included if they directly explored the relationship between Val66Met, obesity, mood, and sleep; were published in English; involved human subjects; and were released within the last decade. Exclusion criteria included animal studies, non-English publications, studies older than 10 years, and those irrelevant to the study objective. Based on these criteria and MeSH keywords, a total of 17 studies were selected: 4 on metabolic outcomes, 3 on sleep and cognitive functions, 3 on emotional and mood-related vulnerabilities, and 7 discussing strategies to enhance BDNF expression.

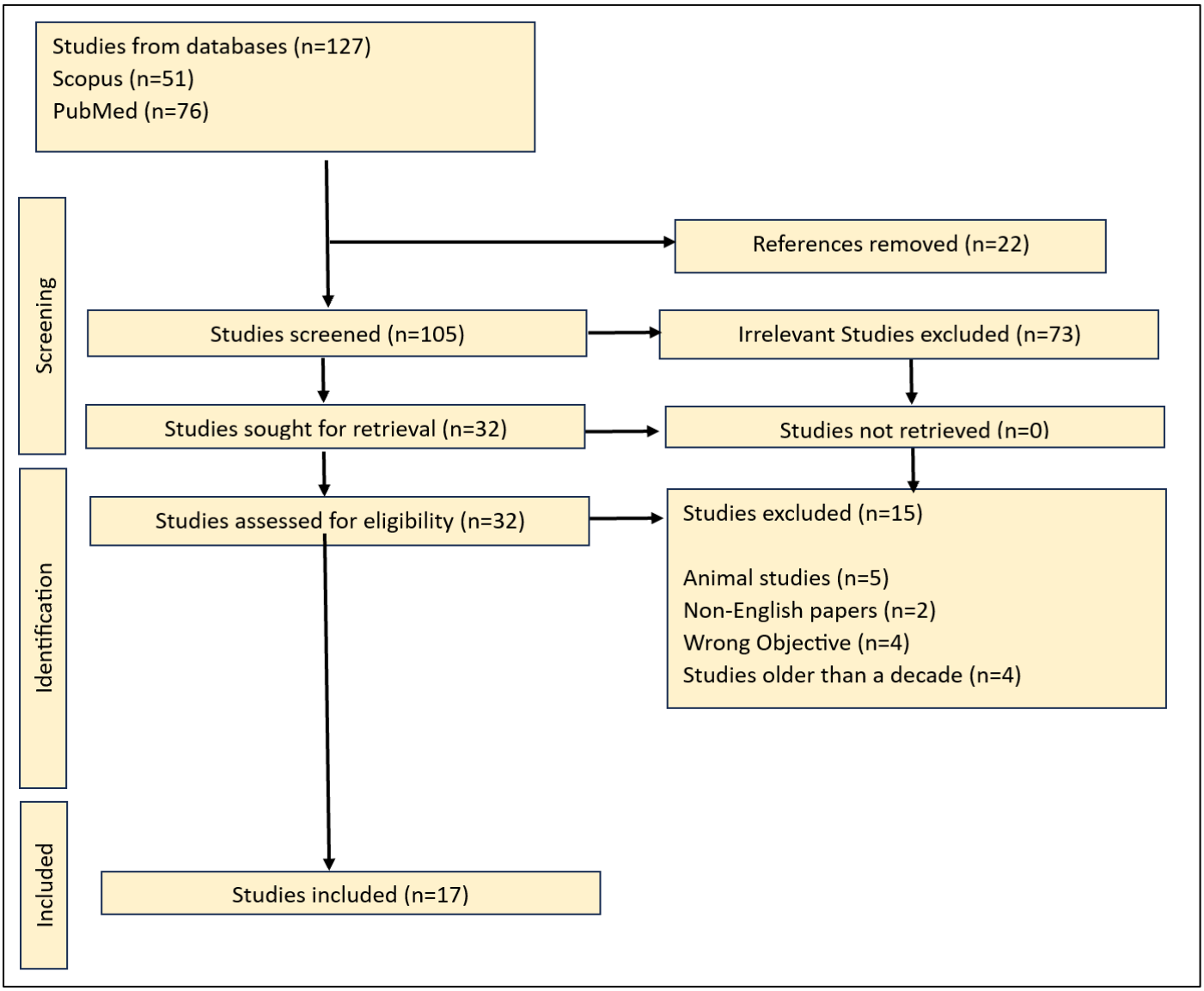

Fig 3 Flow Diagram of Study Selection

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

VII. RESULTS

Table 1 Summary of Studies Investigating Val66Met SNP in Relation to Obesity and Metabolic Outcomes

Objective	Sample	Methodology	Findings	Reference
Val66Met association with obesity in psychiatric patients	166 patients with BPD or SCZ	Prospective trial; genotyping + metabolic assessment (12 months)	Met = ↑BMI and ↑TG/HDL ratio; Met allele may act as a metabolic risk factor	(Bonaccorso et al., 2015)
Val66Met-driven BDNF response to exercise stress	13 healthy male athletes	Gene expression study; muscle biopsy pre/post-VO_2max; BDNF mRNA via ddPCR	Met66 = 1.3× ↓BDNF vs Val66 post-exercise; ↓BDNF transcription in Met allele under stress	(De Assis et al., 2021)
Impact of rs6265 & physical activity on obesity risk	578 (290 OW, 288 NW)	Case-control gene-behavior study; genotyping & single-time assessment of physical activity, WC, BMI via structured questionnaires	Met allele + low activity → ↑WC; Met allele increases obesity risk in presence of low physical activity	(Rana et al., 2021)
Val66Met effects diet & cardiometabolic risk	187 obese adolescents (14–18 years)	Cross-sectional study; genotyping, dietary logs, and baseline metabolic markers	Met = ↑protein/fat intake, ↑CRP, ↓HDL-C vs Val/Val; Val66Met may affect appetite and inflammation in obesity	(Goldfield et al., 2021)

Table 2 Summary of Studies Highlighting the Role of Val66Met Polymorphism in Sleep and Cognitive Functions

Objective	Sample	Methodology	Findings	Reference
Val66Met effects on sleep, cognition, and depression in chronic insomnia	250 (199 insomnia, 51 controls)	Case-control study; genotyping, MoCA, HAM-D, and overnight polysomnography	Met = ↓cognition, ↑depression, ↑sleep disturbances vs Val/Val. Met allele ↑vulnerability to mood and sleep dysfunction	(Zaki et al., 2019)
Val66Met's influence on sleep-dependent memory consolidation	107 older adults (55–84 years); 79 Val/Val, 28 Met	Observational sleep study; polysomnography + cognitive testing (1-night lab study)	Val/Val: ↑memory with better sleep. Met: no benefit from sleep, ↓memory. Met allele impairs sleep-related memory	(Gosselin et al., 2016)
Val66Met linked cognitive changes during sleep deprivation	30 healthy adults (12 Val/Met, 18 Val/Val)	Experimental study; sleep deprivation (30h) with cognitive testing (Stroop task every 2 hours)	Under prolonged sleep deprivation, Met carriers= ↓response accuracy, slow reaction time. Sleep loss + Met→ ↑ executive dysfunction	(Grant et al., 2018)

Table 3 Summary of Studies Examining Val66Met SNP Associated with Emotional and Cognitive Vulnerabilities

Objective	Sample	Methodology	Findings	Reference
Val66Met effect on region-specific BDNF expression in brain	985	Postmortem genotype-expression study; analysis across 5 brain regions using GTEx RNA-seq (cross-sectional)	Val66Met → region specific BDNF expression changes (cerebellum, cortex, caudate); linked to epigenetic risk for MDD, BD, OCD, SCZ, SUD	(Devlin et al., 2021)
Val66Met's impact on white matter network resilience	73 healthy adults (18 Val/Val, 55 Met)	Cross-sectional neuroimaging study; genotyping + DTI with graph theory-based network analysis	Met carriers = ↓white matter resilience, ↑vulnerability to damage. Met allele → mood and cognitive risks	(C. Park et al., 2017)
Val66Met's association with BDNF levels in brain regions involved in depression and suicide	90 (37 suicide decedents, 53 controls)	Postmortem neurobiological study; Western blot for BDNF + genotyping (postmortem analysis)	Met allele = ↓BDNF in anterior cingulate & caudal brainstem. Val66Met → ↑vulnerability to mood disorders and suicide	(Youssef et al., 2018)

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

Table 4 Strategies to Enhance BDNF

Intervention	Mechanism of Action	BDNF ↑/↓	Reference
30 mg/day of elemental zinc for 12 weeks	Activates Trk receptors and MMPs → pro-BDNF converts to mature BDNF; stimulates MAPK/ERK & PI3K/Akt pathways → ↑ BDNF transcription; modulates NMDA, AMPA, serotonin systems; ↓inflammation & OS	Zinc ↑serum BDNF	(Solati et al., 2015)
Folic acid (2 mg) + Methylcobalamin (400 mcg) daily for 8 weeks	↑BDNF expression due to: ↑ methylation and NMDA receptor function; ↓homocysteine and oxidative stress	↑BDNF levels	(Kasir et al., 2023)
BDNF and active Vitamin D levels quantified	Vitamin D ↑BDNF via VDR-mediated gene transcription & serotonin modulation	Vitamin D_3 ↑BDNF	(Dawoud et al., 2023)
20-min cycling: HIT (1 min @90% max work, 1 min rest) vs. CON (70% max, continuous)	HIT → ↑ lactate, leg fatigue, PGC-1α, oxidative stress (e.g., H_2O_2, TNF-α) → ↑ BDNF via neuroplasticity signaling	Both HIT and CON ↑serum BDNF	(Murawska-Ciałowicz et al., 2021)
Measured BDNF/proBDNF levels based on insomnia and cognitive status	Poor sleep = ↓BDNF by acting as a chronic stressor; ↓proBDNF synthesis and conversion into mature BDNF; impairs neuroplasticity and cognitive resilience	Good sleep ↑BDNF	(Sánchez-García et al., 2023)
omega-3 (2400 mg/day: 1000 mg EPA, 750 mg DHA) for 12 weeks	↑BDNF due to: ↓ inflammation via COX pathway; AA displacement; gene modulation, PI3K/Akt pathway activation	Omega-3 ↑BDNF	(Paduchová et al., 2021)
Polyphenol-rich nutraceutical	Polyphenols cross blood–brain barrier → ↓oxidative stress → activate CREB (a transcription factor) → CREB upregulates BDNF gene expression → ↑ BDNF synthesis	Polyphenol ↑BDNF	(Carrillo et al., 2025)

VIII. DISCUSSION

The Val66Met (rs6265) polymorphism in BDNF gene arises from a SNP (G to A) at position 196, resulting in a valine (Val) to methionine (Met) substitution at codon 66 (Behrendt et al., 2024). This genetic variation affects how BDNF is processed and released inside the cell. Specifically, the Met allele reduces the release of BDNF during times of increased neural activity. This decrease in activity-dependent BDNF release limits how much is available at the communication point between neurons and may impact important brain functions (Ryu et al., 2021). The general population sample from the 1000 Human Genome Project showed a prevalence of 33.25% for the Val/Met genotype and 4% for the Met/Met genotype, indicating that a considerable portion of the population carries Met allele (Henechowicz et al., 2021). However, not all Met allele carriers show functional impairments, suggesting that the Met allele alone is insufficient to cause dysfunction and that environmental factors modulate its effects (Martens et al., 2021). Environmental factors such as stress, sleep quality, and diet can interact with genetic predisposition and through mechanisms like DNA methylation and other epigenetic modifications, modulate gene expression, thereby shaping how the Val66Met polymorphism influences physiology and behavior (Komar-Fletcher et al., 2023). These environmentally induced epigenetic changes may alter the transcriptional activity of BDNF, amplifying or buffering the phenotypic effects of the Met allele.

The BDNF Val66Met polymorphism appears to exert pleiotropic effects that influence multiple physiological traits including energy metabolism, mood regulation and potentially sleep, through its shared role in neurobiological circuits such as the hypothalamus and limbic system. The Met allele interferes with release and delivery of mature BDNF, which reduces the activation of its receptor, TrkB, disrupting neural pathways involved in metabolic regulation, reward processing, and inflammatory signaling. This kind of metabolic dysfunction indirectly impacts mood and sleep patterns, since high inflammation (like increased C-reactive protein levels) and energy imbalance are known to disrupt both circadian rhythms and emotional stability. In this way, BDNF Val66Met polymorphism creates a shared vulnerability through impaired BDNF-TrkB signaling across metabolism, mood, and sleep. These domains are closely interconnected as poor sleep can worsen mood and promote weight gain, while depression and obesity often share underlying inflammatory and hormonal imbalance. So, Val66Met may thus serve as a biological link, contributing to clustering of these conditions, particularly in the presence of adverse environmental factors (Goldfield et al., 2021).

Understanding the interaction between BDNF Val66Met SNP and environmental stressors provide critical insight into the variability of phenotypic outcomes. Met carriers may be more responsive to lifestyle-based therapies such as exercise, structured sleep routine, stress management or targeted nutritional support that help buffer the impact of their genetic predisposition.

IX. CONCLUSION

The increased vulnerability highlights the need for strategies that not only enhance BDNF but are also personalized to individual risk profiles. While many studies have looked at how the BDNF Val66Met polymorphism affects obesity, mood disorders, or sleep problems on their own, very few have connected the dots between them. This makes it harder to understand the full picture of how this

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

genetic variation might influence health in a more holistic way. Most of the existing research focuses on isolated effects, rather than exploring how shared biological pathways might explain why these conditions often occur together. There is also a noticeable lack of studies looking at real-world, personalized strategies that could help manage these effects more effectively. This points to the need for more interdisciplinary and integrated research work that can deepen our understanding of the polymorphism's broad impact and guide better, more targeted interventions in the future. Integrating lifestyle and nutritional interventions into a personalized framework represents a promising direction for both preventive and therapeutic strategies targeting BDNF mediated health outcomes.

ABBREVIATIONS

BPD: Bipolar Disorder, SCZ: Schizophrenia, ddPCR: droplet digital PCR, OW: Overweight, NW: Normal Weight, WC: Waist Circumference, MoCA: Montreal Cognitive Assessment, HAM-D: Hamilton Depression Rating Scale, DTI: Diffusion Tensor Imaging, GTEx: Genotype-Tissue Expression, RNA-seq: RNA sequencing; MDD: Major Depressive Disorder, BD: Bipolar Disorder, OCD: Obsessive-Compulsive Disorder, SCZ: Schizophrenia SUD: Substance Use Disorders, OS: oxidative stress, Trk: Tropomyosin receptor kinase, MMPs: Matrix Metalloproteinases, MAPK/ERK: mitogen-activated protein kinase/extracellular signal-regulated kinase, PI3K/Akt: phosphoinositide 3-kinase/Protein kinase B, NMDA: N-methyl-D-aspartate, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, HIT: High-Intensity Training, CON: Continuous Moderate-intensity exercise, PGC-1α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha, H_2O_2: Hydrogen Peroxide, TNF-α: Tumor Necrosis Factor Alpha, VDR: Vitamin D Receptor, COX pathway: Cyclooxygenase pathway, AA: Arachidonic Acid, CREB: cAMP Response Element-Binding Protein

REFERENCES

[1]. Vidović V, Maksimović N, Novaković I, et al. Association of the brain-derived neurotrophic factor Val66Met polymorphism with body mass index, fasting glucose levels and lipid status in adolescents. Balk J Med Genet. 2020;23(1):77-82. doi:10.2478/bjmg-2020-0004

[2]. Devlin P, Cao X, Stanfill AG. Genotype-expression interactions for BDNF across human brain regions. BMC Genomics. 2021;22(1):207. doi:10.1186/s12864-021-07525-1

[3]. Bonaccorso S, Sodhi M, Li J, et al. The brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is associated with increased body mass index and insulin resistance measures in bipolar disorder and schizophrenia. Bipolar Disord. 2015;17(5):528-535. doi:10.1111/bdi.12294

[4]. Saitoh K, Furihata R, Kaneko Y, Suzuki M, Takahashi S, Uchiyama M. Association of serum BDNF levels and the BDNF Val66Met polymorphism with the sleep pattern in healthy young adults. Hashimoto K, ed. PLOS ONE. 2018;13(6):e0199765. doi:10.1371/journal.pone.0199765

[5]. Park KS, Ganesh AB, Berry NT, et al. The effect of physical activity on cognition relative to APOE genotype (PAAD-2): study protocol for a phase II randomized control trial. BMC Neurol. 2020;20(1):231. doi:10.1186/s12883-020-01732-1

[6]. De Assis GG, Hoffman JR, Bojakowski J, Murawska-Ciałowicz E, Cięszczyk P, Gasanov EV. The Val66 and Met66 Alleles-Specific Expression of BDNF in Human Muscle and Their Metabolic Responsivity. Front Mol Neurosci. 2021;14:638176. doi:10.3389/fnmol.2021.638176

[7]. Park C hyun, Kim J, Namgung E, et al. The BDNF Val66Met Polymorphism Affects the Vulnerability of the Brain Structural Network. Front Hum Neurosci. 2017;11:400. doi:10.3389/fnhum.2017.00400

[8]. Rana S, Sultana A, Bhatti AA. Effect of interaction between obesity-promoting genetic variants and behavioral factors on the risk of obese phenotypes. Mol Genet Genomics. 2021;296(4):919-938. doi:10.1007/s00438-021-01793-y

[9]. Honarmand H, Bonyadi M, Rafat A, Mahdavi R, Aliasghari F. Association study of the BDNF gene polymorphism (G196A) with overweight/obesity among women from Northwest of Iran. Egypt J Med Hum Genet. 2021;22(1):7. doi:10.1186/s43042-020-00130-z

[10]. Goldfield GS, Walsh J, Sigal RJ, et al. Associations of the BDNF Val66Met Polymorphism With Body Composition, Cardiometabolic Risk Factors, and Energy Intake in Youth With Obesity: Findings From the HEARTY Study. Front Neurosci. 2021;15:715330. doi:10.3389/fnins.2021.715330

[11]. Youssef MM, Underwood MD, Huang YY, et al. Association of BDNF Val66Met Polymorphism and Brain BDNF Levels with Major Depression and Suicide. Int J Neuropsychopharmacol. 2018;21(6):528-538. doi:10.1093/ijnp/pyy008

[12]. Zhang M, Ward J, Strawbridge RJ, et al. How do lifestyle factors modify the association between genetic predisposition and obesity-related phenotypes? A 4-way decomposition analysis using UK Biobank. BMC Med. 2024;22(1):230. doi:10.1186/s12916-024-03436-6

[13]. Amadio P, Macchi C, Favero C, et al. Brain-Derived Neurotrophic Factor and Extracellular Vesicle-Derived miRNAs in an Italian Cohort of Individuals With Obesity: A Key to Explain the Link Between Depression and Atherothrombosis. Front Cardiovasc Med. 2022;9:906483. doi:10.3389/fcvm.2022.906483

[14]. Desai D, Momin A, Hirpara P, Jha H, Thaker R, Patel J. Exploring the Role of Circadian Rhythms in Sleep and Recovery: A Review Article. Cureus. Published online June 3, 2024. doi:10.7759/cureus.61568

[15]. Zaki NFW, Saleh E, Elwasify M, et al. The association of BDNF gene polymorphism with cognitive impairment in insomnia patients. Prog Neuropsychopharmacol Biol Psychiatry. 2019;88:253-264. doi:10.1016/j.pnpbp.2018.07.025

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

[16]. Gosselin N, De Beaumont L, Gagnon K, et al. BDNF Val66Met Polymorphism Interacts with Sleep Consolidation to Predict Ability to Create New Declarative Memories. J Neurosci. 2016;36(32):8390-8398. doi:10.1523/JNEUROSCI.4432-15.2016

[17]. Mayeli A, Wilson JD, Donati FL, Ferrarelli F. Reduced slow wave density is associated with worse positive symptoms in clinical high risk: An objective readout of symptom severity for early treatment interventions? Psychiatry Res. 2024;333:115756. doi:10.1016/j.psychres.2024.115756

[18]. Muto V, Koshmanova E, Ghaemmaghami P, et al. Alzheimer's disease genetic risk and sleep phenotypes in healthy young men: association with more slow waves and daytime sleepiness. Sleep. 2021;44(1):zsaa137. doi:10.1093/sleep/zsaa137

[19]. Niles AN, Luxenberg A, Neylan TC, et al. Effects of Threat Context, Trauma History, and Posttraumatic Stress Disorder Status on Physiological Startle Reactivity in Gulf War Veterans. J Trauma Stress. 2018;31(4):579-590. doi:10.1002/jts.22302

[20]. Shi J, Guo H, Liu S, et al. Resting-state functional connectivity of neural circuits associated with primary and secondary rewards in patients with bipolar disorder. Soc Cogn Affect Neurosci. 2020;15(7):755-763. doi:10.1093/scan/nsaa100

[21]. Taren AA, Gianaros PJ, Greco CM, et al. Mindfulness meditation training alters stress-related amygdala resting state functional connectivity: a randomized controlled trial. Soc Cogn Affect Neurosci. 2015;10(12):1758-1768. doi:10.1093/scan/nsv066

[22]. Peters RB, Xavier J, Mondin TC, et al. BDNF Val66Met polymorphism and resilience in major depressive disorder: the impact of cognitive psychotherapy. Braz J Psychiatry. 2021;43(1):22-28. doi:10.1590/1516-4446-2019-0726

[23]. West HV, Burgess GC, Dust J, Kandala S, Barch DM. Amygdala Activation in Cognitive Task fMRI Varies with Individual Differences in Cognitive Traits. Cogn Affect Behav Neurosci. 2021;21(1):254-264. doi:10.3758/s13415-021-00863-3

[24]. Puccetti NA, Schaefer SM, Van Reekum CM, et al. Linking Amygdala Persistence to Real-World Emotional Experience and Psychological Well-Being. J Neurosci. 2021;41(16):3721-3730. doi:10.1523/JNEUROSCI.1637-20.2021

[25]. Redlich R, Schneider I, Kerkenberg N, et al. The role of BDNF methylation and Val 66 Met in amygdala reactivity during emotion processing. Hum Brain Mapp. 2020;41(3):594-604. doi:10.1002/hbm.24825

[26]. Fungaro Rissatti L, Wilson D, Palace-Berl F, et al. BDNF methylation associated with stress in women: Novel insights in epigenetics and inflammation. Brain Behav Immun - Health. 2024;42:100900. doi:10.1016/j.bbih.2024.100900

[27]. Rappaport BI, Barch DM. Brain responses to social feedback in internalizing disorders: A comprehensive review. Neurosci Biobehav Rev. 2020;118:784-808. doi:10.1016/j.neubiorev.2020.09.012

[28]. Schmitt K, Holsboer-Trachsler E, Eckert A. BDNF in sleep, insomnia, and sleep deprivation. Ann Med. 2016;48(1-2):42-51. doi:10.3109/07853890.2015.1131327

[29]. Wheeler AL, Felsky D, Viviano JD, et al. BDNF-Dependent Effects on Amygdala–Cortical Circuitry and Depression Risk in Children and Youth. Cereb Cortex. 2018;28(5):1760-1770. doi:10.1093/cercor/bhx086

[30]. Mahindru A, Patil P, Agrawal V. Role of Physical Activity on Mental Health and Well-Being: A Review. Cureus. Published online January 7, 2023. doi:10.7759/cureus.33475

[31]. Lis M, Miłuch T, Majdowski M, Zawodny T. A link between ghrelin and major depressive disorder: a mini review. Front Psychiatry. 2024;15:1367523. doi:10.3389/fpsyt.2024.1367523

[32]. Dakanalis A, Mentzelou M, Papadopoulou SK, et al. The Association of Emotional Eating with Overweight/Obesity, Depression, Anxiety/Stress, and Dietary Patterns: A Review of the Current Clinical Evidence. Nutrients. 2023;15(5):1173. doi:10.3390/nu15051173

[33]. Pietrabissa G, Volpi C, Bottacchi M, et al. The Impact of Social Isolation during the COVID-19 Pandemic on Physical and Mental Health: The Lived Experience of Adolescents with Obesity and Their Caregivers. Int J Environ Res Public Health. 2021;18(6):3026. doi:10.3390/ijerph18063026

[34]. McCartan CJ, Yap J, Firth J, et al. Factors that influence participation in physical activity for anxiety or depression: a synthesis of qualitative evidence. Cochrane Common Mental Disorders Group, ed. Cochrane Database Syst Rev. Published online March 4, 2020. doi:10.1002/14651858.CD013547

[35]. Denche-Zamorano Á, Franco-García JM, Carlos-Vivas J, et al. Increased Risks of Mental Disorders: Youth with Inactive Physical Activity. Healthcare. 2022;10(2):237. doi:10.3390/healthcare10020237

[36]. Konttinen H. Emotional eating and obesity in adults: the role of depression, sleep and genes. Proc Nutr Soc. 2020;79(3):283-289. doi:10.1017/S0029665120000166

[37]. Zhao M, Chen L, Yang J, et al. BDNF Val66Met polymorphism, life stress and depression: A meta-analysis of gene-environment interaction. J Affect Disord. 2018;227:226-235. doi:10.1016/j.jad.2017.10.024

[38]. Xiong HY, Hendrix J, Schabrun S, et al. The Role of the Brain-Derived Neurotrophic Factor in Chronic Pain: Links to Central Sensitization and Neuroinflammation. Biomolecules. 2024;14(1):71. doi:10.3390/biom14010071

[39]. Hiser J, Koenigs M. The multifaceted role of the ventromedial prefrontal cortex in emotion, decision making, social cognition, and psychopathology. Biol Psychiatry. 2018;83(8):638-647. doi:10.1016/j.biopsych.2017.10.030

[40]. Martínez-Ezquerro JD, Rendón-Macías ME, Zamora-Mendoza G, et al. Association Between the Brain-derived Neurotrophic Factor Val66Met Polymorphism and Overweight/Obesity in Pediatric

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

Population. Arch Med Res. 2017;48(7):599-608. doi:10.1016/j.arcmed.2018.02.005
[41]. Kambestad OB, Sirevåg K, Mrdalj J, et al. Cogn Behav Neurol. 2023;36(4).
[42]. Jeon YK, Ha CH. The effect of exercise intensity on brain derived neurotrophic factor and memory in adolescents. Environ Health Prev Med. 2017;22(1):27. doi:10.1186/s12199-017-0643-6
[43]. Furihata R, Saitoh K, Otsuki R, et al. Association between reduced serum BDNF levels and insomnia with short sleep duration among female hospital nurses. Sleep Med. 2020;68:167-172. doi:10.1016/j.sleep.2019.12.011
[44]. Fan TT, Chen WH, Shi L, et al. Objective sleep duration is associated with cognitive deficits in primary insomnia: BDNF may play a role. Sleep. 2019;42(1). doi:10.1093/sleep/zsy192
[45]. Monteiro BC, Monteiro S, Candida M, et al. Relationship Between Brain-Derived Neurotrofic Factor (Bdnf) and Sleep on Depression: A Critical Review. Clin Pract Epidemiol Ment Health. 2017;13(1):213-219. doi:10.2174/1745017901713010213
[46]. Zhang X, Qiao Y, Wang M, et al. The influence of genetic and acquired factors on the vulnerability to develop depression: a review. Biosci Rep. 2023;43(5):BSR20222644. doi:10.1042/BSR20222644
[47]. Godos J, Micek A, Currenti W, et al. Fish consumption, cognitive impairment and dementia: an updated dose-response meta-analysis of observational studies. Aging Clin Exp Res. 2024;36(1):171. doi:10.1007/s40520-024-02823-6
[48]. Agh F, Honarvar NM, Djalali M, et al. Brain-derived neurotrophic factor is increased by omega-3 fatty acids in coronary artery disease: A randomized, double-blind, placebo-controlled. Fat Acids. (1).
[49]. Patted PG, Masareddy RS, Patil AS, Kanabargi RR, Bhat CT. Omega-3 fatty acids: a comprehensive scientific review of their sources, functions and health benefits. Future J Pharm Sci. 2024;10(1):94. doi:10.1186/s43094-024-00667-5
[50]. Maares M, Haase H. A Guide to Human Zinc Absorption: General Overview and Recent Advances of In Vitro Intestinal Models. Nutrients. 2020;12(3):762. doi:10.3390/nu12030762
[51]. Jafari F, Amani R, Tarrahi MJ. Effect of Zinc Supplementation on Physical and Psychological Symptoms, Biomarkers of Inflammation, Oxidative Stress, and Brain-Derived Neurotrophic Factor in Young Women with Premenstrual Syndrome: a Randomized, Double-Blind, Placebo-Controlled Trial. Biol Trace Elem Res. 2020;194(1):89-95. doi:10.1007/s12011-019-01757-9
[52]. De Vargas LDS, Jantsch J, Fontoura JR, Dorneles GP, Peres A, Guedes RP. Effects of Zinc Supplementation on Inflammatory and Cognitive Parameters in Middle-Aged Women with Overweight or Obesity. Nutrients. 2023;15(20):4396. doi:10.3390/nu15204396
[53]. Solati Z, Jazayeri S, Tehrani-Doost M, Mahmoodianfard S, Gohari MR. Zinc monotherapy increases serum brain-derived neurotrophic factor (BDNF) levels and decreases depressive symptoms in overweight or obese subjects: A double-blind, randomized, placebo-controlled trial. Nutr Neurosci. 2015;18(4):162-168. doi:10.1179/1476830513Y.0000000105
[54]. Edmands WM, Ferrari P, Rothwell JA, et al. Polyphenol metabolome in human urine and its association with intake of polyphenol-rich foods across European countries. Am J Clin Nutr. 2015;102(4):905-913. doi:10.3945/ajcn.114.101881
[55]. Pontifex MG, Malik MMAH, Connell E, Müller M, Vauzour D. Citrus Polyphenols in Brain Health and Disease: Current Perspectives. Front Neurosci. 2021;15:640648. doi:10.3389/fnins.2021.640648
[56]. Morton L, Paton C, Braakhuis A. The Effects of Polyphenol Supplementation on BDNF, Cytokines and Cognition in Trained Male Cyclists following Acute Ozone Exposure during High-Intensity Cycling. Nutrients. 2024;16(2):233. doi:10.3390/nu16020233
[57]. Kasir NR, Teddy LS, Irfan I, Abdul M, Erlyn L, Saidah S. EFFECT OF FOLIC ACID AND METHYLCOBALAMIN ADJUVANT THERAPY ON IMPROVEMENT OF CLINICAL SYMPTOMS AND BDNF LEVELS OF IN SCHIZOPHRENIA PATIENTS. 2023;30(17).
[58]. Ledowsky C, Mahimbo A, Scarf V, Steel A. Women Taking a Folic Acid Supplement in Countries with Mandatory Food Fortification Programs May Be Exceeding the Upper Tolerable Limit of Folic Acid: A Systematic Review. Nutrients. 2022;14(13):2715. doi:10.3390/nu14132715
[59]. Al Zoubi MS, Al Kreasha R, Aqel S, Saeed A, Al-Qudimat AR, Al-Zoubi RM. Vitamin B12 deficiency in diabetic patients treated with metformin: A narrative review. Ir J Med Sci 1971 -. 2024;193(4):1827-1835. doi:10.1007/s11845-024-03634-4
[60]. Quialheiro A, D´Orsi E, Moreira JD, Xavier AJ, Peres MA. The association between vitamin D and BDNF on cognition in older adults in Southern Brazil. Rev Saúde Pública. 2022;56:109. doi:10.11606/s1518-8787.2022056004134
[61]. Dawoud NM, Rajab AZ, El-Hefnawy SM, El-Bayoumy AM, Salem AM, Seleit I. Serum brain-derived neurotrophic factor and vitamin D: Two concordant players controlling depression among alopecia areata and vitiligo patients: A case–control study. J Cosmet Dermatol. 2023;22(8):2343-2351. doi:10.1111/jocd.15725
[62]. Dominguez LJ, Farruggia M, Veronese N, Barbagallo M. Vitamin D Sources, Metabolism, and Deficiency: Available Compounds and Guidelines for Its Treatment. Metabolites. 2021;11(4):255. doi:10.3390/metabo11040255
[63]. Grant LK, Cain SW, Chang AM, Saxena R, Czeisler CA, Anderson C. Impaired cognitive flexibility during sleep deprivation among carriers of the Brain Derived Neurotrophic Factor (BDNF) Val66Met allele. Behav

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul511

Brain Res. 2018;338:51-55. doi:10.1016/j.bbr.2017.09.025

[64]. Murawska-Ciałowicz E, De Assis GG, Clemente FM, et al. Effect of four different forms of high intensity training on BDNF response to Wingate and Graded Exercise Test. Sci Rep. 2021;11(1):8599. doi:10.1038/s41598-021-88069-y

[65]. Sánchez-García S, Moreno-Tamayo K, Ramírez-Aldana R, et al. Insomnia Impairs Both the Pro-BDNF and the BDNF Levels Similarly to Older Adults with Cognitive Decline: An Exploratory Study. Int J Mol Sci. 2023;24(8):7387. doi:10.3390/ijms24087387

[66]. Paduchová Z, Katrenčíková B, Vaváková M, et al. The Effect of Omega-3 Fatty Acids on Thromboxane, Brain-Derived Neurotrophic Factor, Homocysteine, and Vitamin D in Depressive Children and Adolescents: Randomized Controlled Trial. Nutrients. 2021;13(4):1095. doi:10.3390/nu13041095

[67]. Carrillo JÁ, Arcusa R, Xandri-Martínez R, Cerdá B, Zafrilla P, Marhuenda J. Impact of Polyphenol-Rich Nutraceuticals on Cognitive Function and Neuroprotective Biomarkers: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Nutrients. 2025;17(4):601. doi:10.3390/nu17040601

[68]. Behrendt T, Quisilima JI, Bielitzki R, et al. Brain-Derived neurotrophic factor and inflammatory biomarkers are unaffected by acute and chronic intermittent hypoxic-hyperoxic exposure in geriatric patients: a randomized controlled trial. Ann Med. 2024;56(1):2304650. doi:10.1080/07853890.2024.2304650

[69]. Ryu JS, Lee YM, Kim YS, et al. Association between BDNF Polymorphism and Depressive Symptoms in Patients Newly Diagnosed with Type 2 Diabetes Mellitus. Yonsei Med J. 2021;62(4):359. doi:10.3349/ymj.2021.62.4.359

[70]. Henechowicz TL, Chen JL, Cohen LG, Thaut MH. The prevalence of the Val66Met polymorphism in musicians: Possible evidence for compensatory neuroplasticity from a pilot study. Li Z, ed. PLOS ONE. 2021;16(6):e0245107. doi:10.1371/journal.pone.0245107

[71]. Martens L, Herrmann L, Colic L, et al. Met carriers of the BDNF Val66Met polymorphism show reduced Glx/NAA in the pregenual ACC in two independent cohorts. Sci Rep. 2021;11(1):6742. doi:10.1038/s41598-021-86220-3

[72]. Komar-Fletcher M, Wojas J, Rutkowska M, Raczyńska G, Nowacka A, Jurek JM. Negative environmental influences on the developing brain mediated by epigenetic modifications. Explor Neurosci. 2023;2(5):193-211. doi:10.37349/en.2023.00021