

The Impact of Intermittent Fasting as an Adjuvant Therapeutic Intervention for Major Depressive Disorder: A Literature Review

Fauziyyah Shofura Yasmin^{1*}, Nadia Taqiya², Hasna Nurul Alya³

ABSTRACT

Introduction: Intermittent fasting has previously been studied as an adjuvant therapeutic option in alleviating the symptoms of major depressive disorder. This literature review will discuss the mechanism in which intermittent fasting affects major depressive disorder. **Methods:** Relevant journal articles from the past 5 years were searched through PubMed, Google Scholar, and ClinicalKey. **Results:** Research has shown that intermittent fasting alleviates the symptoms of depression through metabolic response mechanisms, increases in neurotransmitters and the neurotrophic BDNF, changes in the circadian rhythm, the hypothalamus-pituitary-adrenal (HPA) axis, and changes to the diet a gut microbiome. The intermittent fasting protocols vary by study; therefore, the most effective method should be ascertained. **Conclusion:** The results of several studies show a positive correlation between intermittent fasting and the alleviation of the symptoms of major depressive disorder. Additional research is needed to determine which method of intermittent fasting can most effectively be integrated as an adjuvant therapeutic option for major depressive disorder.

Keywords: major depressive disorder, intermittent fasting

-
1. Klinik Utama An-Nur, Purwokerto, Indonesia
 2. Puskesmas Gambir, Jakarta Pusat, Indonesia
 3. Puskesmas Pulau Beringin, Ogan Komering Ulu Selatan, Indonesia
- *✉ email: fauziyyahshofuray@gmail.com

INTRODUCTION

Major depressive disorder (MDD) is a mental health disorder characterised by an intense and persistent feeling of sadness, or by a lack of interest in external stimuli. This condition can significantly impair day-to-day functioning, negatively impacting a patient's career, social interactions, and quality of life in general. An MDD diagnosis requires five or more symptoms, which include changes to the sleeping pattern, changes to the diet, fatigue, difficulty in concentration, excessive feelings of guilt, psychomotor slowing or agitation, and persistent ideation of death or suicide for a period of two weeks or more. Moreover, at least one symptom has to be a lowered mood or anhedonia¹.

The Association of Southeast Asian Nations (ASEAN) reported 80.4 million cases of mental health disorders in 2021 with the highest number being from Indonesia with 32.9 million cases. MDD was the second-most common mental health disorder in ASEAN with 21.3 million cases. Antidepressants are the therapeutic gold-standard for MDD. However, some studies have found that antidepressants are only effective in half the cases and often cause adverse side effect, thus there is a need to have a supportive (adjuvant) intervention to

optimize treatment. Physiological pathways such as the gut-brain axis plays a role in alleviating the symptoms of MDD as it relates to gut microbiome. The field of psychonutrition has been evolving alongside newer research regarding the protective role of healthy/anti-inflammatory diets against MDD. Lifestyle modifications such as towards nutrition has been found to be a viable therapeutic target for mental health therapy and for increasing cognitive function. Several studies have showcased the potential positive effects of intermittent fasting (IF) on the mood through its effects on metabolic responses, neurotransmitters, an increase in neurotrophic synthesis, the circadian rhythm, and the composition of gut microbiome²⁻⁵.

IF is defined as a dietary pattern that limits ad libitum eating time — not the amount or the composition of food — that doesn't result in malnutrition. IF protocols vary; most of the IF protocols reported in literature can be classified into several main categories, which are alternate day fasting (ADF; fasting every other day), whole-day fasting (1–2 days of fasting a week), time-restricted feeding (TRF; time-limited consumption of calories in 8–12 hour periods), fasting-mimicking diets (periodic cycle of 5 days of low-calorie intake with an ad

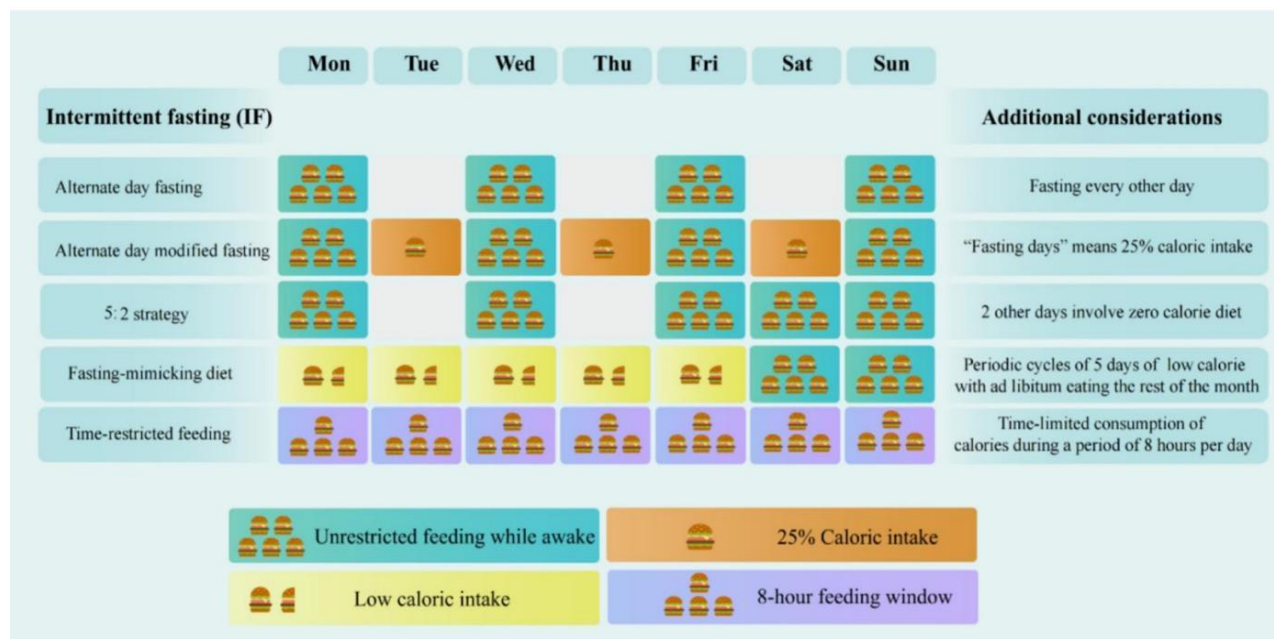


Figure 1. Conceptual Illustration of Intermittent Fasting⁷

libitum diet for the rest of the month), and periodic fasting (5 days of an ad libitum diet followed by 2 days of fasting)^{6,7}.

Several studies have found that as a nutritional intervention, IF is beneficial towards mental health, alleviating the symptoms of MDD and anxiety. IF has been found to improve the cognitive-affective subscores of MDD patients with severe symptoms that had previously not responded to pharmacological therapy. The mechanism in which IF improves mood is by the metabolism of glucose into ketone bodies, anti-inflammatory effects, anti-oxidative effects, stress-resistant effects, gut microbiome alteration and reduction of inflammation of the gut by avoiding inflammation-inducing foods and reducing blood flow to the gut, and increasing the availability of neurotransmitters and neurotrophic factor in the brain. Ketone plays a role as an alternative energy source for the brain during fasting, thus an increase in ketone concentrations can improve brain metabolism and can modulate the expression of brain-derived neurotrophic factor (BDNF)⁹.

The duration of IF also plays a role on the desired effects. Short-term IF (around 8 weeks) can improve the gut barrier and lower systemic inflammation, whereas long-term IF (around 12 weeks) can have a more substantial effect on neurotrophic factors and cognitive function. The effectiveness of IF varies and is dependent on the presence of disease and individual characteristics. For example, ADF shows higher effectiveness for metabolic disturbances, whereas TRF is more beneficial for neurological conditions that are associated with circadian rhythm disturbances. Individuals on a TRF diet more rarely show symptoms of mental health disorder, and individuals on a consistent IF diet have a higher potential life expectancy unburdened by cognitive decline in comparison to individuals that are inconsistent in their diet or not on a diet at all^{2,9}.

If IF is maintained for a long period of time, a process known as “flipping the metabolic switch” is initiated. This process

occurs around 12 to 36 hours after the fasting was initiated, and depends on the reserve of glycogen in the liver, the composition of the food consumed previously, and the total energy expended by the individual throughout the fast. Flipping the metabolic switch entails the body switching from the process of glycogenolysis (the breakdown of glycogen into glucose) to lipolysis (the use of fat stored in the form of lipids from adipose tissue). The released lipids are then metabolised into free fatty acids (FFAs) and then transformed into ketones. Other than being a source of energy, ketones also affect the transcription factor in neurons. This metabolic process increases the concentration of BDNF. Moreover, IF also reduces inflammation — overreaction from the body towards injuries or infections — by reducing the amount of pro-inflammatory monocytes and other white blood cells in the blood. IF also has the positive indirect effect on the brain of increasing insulin sensitivity. The lowered insulin in the blood increases the sensitivity of insulin receptors and enhances the insulin-like growth factor-1/IGF-1 signaling (IIS) pathways, thus increasing absorption and utilisation of glucose in neurons, which is associated with an increase in neuroplasticity and protection against oxidative stress¹³.

Given that neurotransmission and neuroplasticity as the main targets of antidepressants are highly dependent on energy availability, modulating the availability of energy through fasting can potentially increase the effectiveness of conventional therapy. Thus, fasting can be considered as a promising augmenting strategy, specifically for MDD patients that do not sufficiently respond to guideline-based therapy⁹. This literature review will comprehensively discuss the mechanism in which IF affects MDD.

METHODS & MATERIALS

The research method used in this study is a literature review on intermittent fasting as a nonpharmacological therapeutic option for major depressive disorder. The search was

performed using the databases of PubMed, Google Scholar, and ClinicalKey. The keywords used were “major depressive disorder” and “intermittent fasting”. The literature that was included were journals published in English within the last 5 years.

REVIEWS

Research regarding the effects of IF on MDD has not been plentiful. Most of the studies obtained for this review only indirectly mention the effects of IF on MDD. Several studies found different results and outcome depending on the type and duration of the IF protocol. IF was not found to have any short-term benefit on cognition for healthy individuals, although there are indications that IF can be a protective

measure against neurological disorders. Maintenance of neuroplasticity requires adequate energy and several studies have found that calorie restriction improves the function and structure of the hippocampus whereas a high-calorie diet has the opposite effect, which is in accordance with a study which found that radiological imaging shows a metabolic disturbance in the brain in MDD patients. A study that used a Ramadhan fast as an intervention found that it reduces the symptoms of MDD, anxiety, and stress. Another study has also confirmed that a Ramadhan fast reduces the symptoms of MDD, anxiety, and stress in individuals in comparison to before fasting^{4,9,10,13}.

Table 1. Studies regarding the effects of intermittent fasting on major depressive disorder

Authors	Titles	Study Design	Results
Sharifi et al, 2024	Effect of time-restricted eating and intermittent fasting on cognitive function and mental health in older adults: a systematic review	Systematic review	IF and TRE are correlated with cognitive function and mental health in geriatrics
Berthelot et al, 2021	Fasting Interventions for Stress, Anxiety and Depressive Symptoms: A Systematic Review and Meta-Analysis	Systematic Review and Meta-Analysis	The fasting intervention group (including IF and TRE) had a lower level of anxiety, depression, and body mass index in comparison to the control group
Murta et al, 2023	Intermittent Fasting as a Potential Therapeutic Instrument for Major Depression Disorder: A Systematic Review of Clinical and Preclinical Studies	Systematic Review of Clinical and Preclinical Studies	TRF is the most effective type of fasting intervention for controlling mood, as it synchronises eating intervals with the circadian rhythm
Mayor, 2023	Neurotrophic effects of intermittent fasting, calorie restriction and exercise: a review and annotated bibliography.	Narrative review and annotated bibliography	IF and calorie restriction can increase the expression of neurotrophic factors such as BDNF and can increase neurogenesis which has a positive impact on long-term brain health especially when implemented as a therapy for MDD
Lv, 2025	Intermittent fasting and neurodegenerative diseases: Molecular mechanisms and therapeutic potential	Narrative review	IF intervention impacts metabolic responses, inflammation processes, and mitochondrial metabolism which affects mood regulation including in MDD
Rabiei, 2025	The Association of Different Types of Intermittent Fasting	Systematic review and	IF can potentially alleviate symptoms of MDD and anxiety by increasing GABA

Authors	Titles	Study Design	Results
	with Mental Health: A Protocol for Systematic Review.	meta analysis	inhibitors, modulating excitatory glutamate pathways, increasing neurotrophic BDNF concentrations, increasing serotonin concentrations through activation of the HPA axis, and activating the main metabolic sensors in the brain. The effects of Ramadhan fasting on mental health is mediated by psychoneuroendocrine mechanisms such as the release of growth hormones which can reduce stress and anxiety
Stapel et al, 2022	Impact of fasting on stress systems and depressive symptoms in patients with major depressive disorder: a cross-sectional study	Cross-sectional study	Fasting interventions improve cognitive-affective subscores of MDD patients with moderate/severe symptoms that had previously not responded to therapy. Intervention that directly modulate energy metabolism improves cognitive-affective symptoms and/or increases therapeutic efficacy for patients with moderate to severe MDD.
Yousuf et al, 2021	To explore the association of Ramadan fasting with symptoms of depression, anxiety, and stress in people with diabetes	Observational study	There was an improvement in the symptoms of MDD, anxiety, and stress in diabetic patients post-Ramadhan fasting
Wang and Wu, 2022	The effect of fasting on human metabolism and psychological health	Narrative review	IF is correlated with mood regulation and decreased the symptoms of MDD
Zhao et al, 2025	Effects of intermittent fasting on brain health via the gut-brain axis	Narrative review	IF improves mood regulation by altering the gut microbiome which affects the gut-brain axis. IF balances the Firmicutes-to-Bacteroidetes ratio which has been correlated with remission of anxiety and MDD. The gut-brain axis is an important mediator, in which short chain fatty acids and derivatives of tryptophan increases the synthesis of serotonin and reduces oxidative stress. IF also modulates the gut-microbiota-metabolite-brain axis in order to improve neuroprotection which is beneficial to mental health
Gudden et al, 2021	The Effects of Intermittent Fasting on Brain and Cognitive Function	Narrative review	IF affects the symptoms of MDD through neurotransmitter regulation
Chaix et al, 2019	Time-restricted eating to prevent and manage chronic metabolic diseases	Narrative review	TRE improves mental health through the circadian rhythm and metabolic processes

Authors	Titles	Study Design	Results
de Cabo and Mattson, 2019	Effects of intermittent fasting on health, aging, and disease	Narrative review	IF can be a supportive therapeutic option by increasing neuroplasticity. Eating within a 6-hour period and fasting for 18-hours triggers the transition of metabolism from glucose-based energy to ketone-based energy, which results in an increased stress resistance, a longer life expectancy, and a lowered risk of degenerative diseases including cancer and obesity
Patsalos et al, 2021	Diet, Obesity, and Depression: A Systematic Review	Systematic review	Dietary interventions including IF can potentially be an adjuvant therapeutic option to alleviate the symptoms of depression

Metabolic Response

A metabolic response during fasting which affects the metabolism of lipids, glucose, proteins, and neuroendocrines. IF can lower blood lipid concentrations through glycogenolysis and lipolysis. This metabolic process occurs when the glycogen within hepatocytes is depleted (12–36 hours after initiation of fasting) along with an increased rate of lipolysis in adipose tissues. This process increases the plasma concentration of FFAs which is in order to produce ketones derived from the liver, kidneys, astrocytes, and enterocytes as a source of energy. In diabetic patients that underwent an 8-week alternate-day fasting program, there was a significant decrease of fasting glucose levels, along with a decreased insulin concentration although not statistically significant. IF indirectly has a positive effect on the brain through an increased insulin sensitivity. Insulin sensitivity generally decreases in diabetics, and can also naturally decrease along with age. The decrease of blood insulin concentration can increase the sensitivity of insulin receptors and enhances the IIS pathways which increases the absorption and utilisation of glucose within neurons. The enhanced IIS pathway activity also lowers the activity mechanistic Target of Rapamycin (mTOR) pathway and increases neuroplasticity and protection against oxidative

stress. Studies have also found that early time-restricted feeding (eTRF; 6 hour eating period, with the previous day's dinner time being before 15:00) for a period of 5 weeks increases insulin sensitivity and responsiveness of pancreatic β cells in prediabetic patients. The effect of IF on glucose metabolism is thus inconsistent, dependent on the fasting window, the duration of fasting, and an individual's base characteristics^{11,13}.

Protein metabolic responses show that during fasting, proteins are oxidised and broken down to produce energy. The type and duration of fasting affect the changes to amino acids. Plasma lactic acid, total amino acids, and the total number of essential amino acids are significantly reduced starting at the 3rd hour of fasting. The concentration of glycerides, FFAs, β -hydroxybutyrates (BHBs), and acetoacetic (AcAc) acids significantly increase during fasting, whereas arginines, alanines, serines, threonines, aspartic acids, and prolines significantly decrease. On the other hand, a fasting period of over 16 days can decrease serum concentrations of norepinephrine, epinephrine, and dopamine which are typically induced by exercise. Moreover, a prolonged fast may increase the concentration of glucagon and decrease the concentration of thyrotropins and T3/T4. The release and exchange of serotonin increases

during prolonged fasting. The concentration of plasma β -endorphin significantly increases in individuals that fast for 5–10 days. In rodents, fasting has been found to increase neuropeptide Y genomic expression in certain parts of the brain¹¹.

Neurotrophics and Neurotransmitters

Several studies have found that fasting results in changes to neurotrophic factors and to neurotransmitters. Fasting can stimulate neurogenesis and an increased synaptic plasticity which affects the sensation of pain, cognitive function, and antiaging factor of the brain. The release of serotonin and turnover rates increase during fasting. The increased activity of the serotonergic system results in an improved mood and a reduced pain sensitivity. Rat studies have found tryptophan and an increased concentration of serotonin in the brain during fasting. Moreover, the increased concentration of BDNFs may also be correlated with the central serotonergic regulation system. Other studies have also shown that BDNFs and serotonergic signals have a linear correlation; BDNFs increase the production and release of serotonin. In a study that compared the effects of a 72-hour IF protocol to a water-only protocol in patients with MDD, it was found that IF improved the cognitive-affective subscores in patients with moderate-severe symptoms which had previously not responded to pharmacological therapy. This finding is correlated with the increased concentration of BDNF, which indicates involvement of neuroplasticity mechanisms. The increased concentration of ketones during fasting — which acts as an alternative source of energy for the brain — is suspected to play a role in improving cerebral energy metabolism and in modulating the expression of BDNF^{9,11}.

When IF is maintained for a sufficient amount of time, a metabolic process begins. This process occurs 12 to 36 hours after fasting is initiated, and is dependent on the store of glycogen in the liver, the composition of the previous meal, and the total expenditure of energy during fasting. Under this condition, the body switches from the process of

glycogenolysis (the breakdown of glycogen into glucose) to lipolysis (the use of fat stored in the form of lipids from adipose tissue). Next, the released lipids are metabolised into FFAs which are turned into acetyl-coenzyme A (acetyl CoA) through a process of β -oxidation which are turned into BHBs and AcAcs. Ketones have the additional benefit as a modulator for transcription factors (e.g., CREB or PGC1 α) in neurons. BHB and AcAc are transported from the liver to the brain where they are re-metabolised into acetyl CoA and HMG-CoA which increases the concentration of BDNF. In animal models, the decreased concentration of glucose during IF decreases the ATP:AMP ratio in neurons, which within hours of fasting activates the kinases AMPK and CaMKII. The activation of precursor transcription factor (CREB and PGC1 α) enables the aforementioned kinases to hinder anabolic processes, hindering cell growth and protein biosynthesis. This in turn triggers cell repair by triggering autophagy, a process in which neurons remove dysfunctional or nonfunctional components¹³.

Neurons can regulate protein synthesis as a response to fluctuating nutritional stores via the mTOR pathway. When not fasting, the activation of the mTOR pathway causes protein and lipid synthesis. Conversely, the activation of the mTOR pathway during fasting is reduced, and reducing global protein synthesis and dysfunctional protein recycling via autophagy. Autophagy also plays a role in the body's ability to manage oxidative stress (the dangerous accumulation of free radicals) which worsens along with age and along with the development of neurodegenerative diseases. The reduced activation of the mTOR pathway can increase the availability of antioxidants (molecules that prevent the oxidation of free radicals), repair DNA, and stimulate BDNF production. Moreover, IF also reduces inflammation — overreaction from the body towards injuries or infections — by reducing the amount of pro-inflammatory monocytes and other white blood cells in the blood¹³.

The Circadian Rhythm

The circadian rhythm regulates several physiologically important processes, including the sleep-wake cycle, hormone secretion, energy metabolism, and neurocognitive function. Disruption of the circadian rhythm often found in MDD patients is correlated with sleep disorders, HPA axis dysregulation, increased inflammation, and decreased neuroplasticity. Epidemiological and clinical evidence show that an irregular eating schedule also contributes to circadian rhythm disruption and a decline in mental health¹³.

The circadian rhythm is a 24-hour biological rhythm which is a result of an endogenous circadian clock. This circadian clock regulates the utilisation of nutritional stores on a cellular level and also regulates dietary consumption on a behavioral level. This regulatory process has three main functions; first, when an individual eats at an anticipated time the circadian clock and sensory-nutritional pathways work together to maintain nutritional homeostasis; second, when an individual eats at an unanticipated time the sensory-nutritional pathway manipulates the circadian clock to adjust to the newer eating time thus the next meal is anticipated at that newer time; and third, the circadian rhythm ensures an eating time that is optimal for nutritional absorption thereby avoiding an overload of nutrition. In short, this interaction determines a limited eating window to ensure an optimal metabolism¹⁴.

Thus, TRF — wherein food is consumed in consistent 8–12 hour intervals — has become a dietary intervention which has the potential to restore circadian rhythm synchronisation by limiting food consumption in a certain window of time without the need to reduce total calorie consumption. TRF has been proven to re-synchronise peripheral circadian rhythms including in metabolic tissues and the gut microbiome which plays a role in gut-brain axis communication and mood regulation. IF induces metabolic stress which activates the stress system which includes the HPA axis and the sympathetic nervous system,

which is known to be dysregulated in MDD^{9,12,14}.

Hypothalamic-Pituitary-Adrenal (HPA) Axis

Fasting triggers a metabolic stress response which activates the stress system (HPA axis, renin-angiotensin-aldosterone system, sympathetic activation), which is known to be dysregulated in MDD. Acutely (<24 hours), glycogen thinning activates the HPA axis, which increases the concentration of ACTH and cortisol in order to mobilise glucose and FFAs. Thus, fasting can affect MDD via the aforementioned pathways. This is in accordance with a study that reported an increased cortisol concentration in the cerebrospinal fluid and plasma of an MDD patient after fasting which indicates an increased activity of the HPA axis⁹.

Gut Microbiome

The gut microbiome interacts with the central nervous system via the immunological, endocrinal, and neurological signaling pathways. The gut microbiome activates the sympathetic and parasympathetic pathways in the gut, maintains the gut immune system, and regulates several neurotransmitters and toxins in the gut. Preclinical trials in animal with anxiety and depression have found a disturbance of the gut microbiome. Conditions such as MDD are correlated with a change in gut microbiome taxonomy and microbial metabolites. Thus, by affecting the gut-brain axis, mental disorders can be prevented or treated through modifying available neuroactive metabolite types and modifying certain neuronal transmissions. IF can increase the information exchange of the gut-brain axis by modifying the composition of the gut microbiome and the microbial metabolism, which results in a neuroprotective effect. IF or fasting for 12–16 hours a day can improve gut microbiome, thus improving mental health and reducing the symptoms of MDD¹².

Diet

Lifestyle modification, particularly a nutritional strategy can decrease the risk of MDD. Several studies have found that a Mediterranean diet and its derivatives are

currently the most effective option that has thus far been evaluated. Moreover, a study that evaluated low-carbohydrate diets and ketogenic diets reported a potential benefit in improving and maintaining mood in individuals with mood disorders. Within the last two decades, several studies have shown that IF is a viable nutritional intervention to improve physical and mental health⁵.

A study which analysed the habit of eating a traditional Mediterranean diet — a diet prioritising plant-based foods and healthy fats — found that a diet rich in vegetables, whole seeds, red fruits, nuts, and olive oil along with a low amount of animal protein has a consistently positive impact on MDD patients. Thus, the quality of the diet itself — not just the caloric value — can have a significant impact on mood, which will be an important variable to be considered in clinical studies involving IF⁵.

In IF studies on humans, a noontime fast with a nightly eating schedule such as in a Ramadhan fast (RF) has an anti-physiological effect on the circadian rhythm. Studies on RF found in some individuals a reduced mood and a reduced concentration of blood BDNF which may be caused by a mismatch with circadian regulation⁵.

Alternate theories state that the importance of synchronisation between the circadian rhythm and eating windows indicates that TRF may be the most effective fasting paradigm for mental health and mood regulation, as TRF properly synchronises eating intervals with the circadian rhythm. TRF more efficiently causes weight loss and lowers body fat, both of which are correlated with a significant increase in fatigue and MDD symptoms. Interventions longer than 12 weeks showed better results in parameters measuring mood, which indicates that physiological adaptations triggered by TRF needs sufficient time to occur⁵.

Limitations

Several limitations need to be considered when interpreting findings regarding IF as an additional therapeutic option for MDD symptoms. Evidence is still limited by the

relatively low amount of randomized controlled trials (RCTs) conducted thus far, particularly on clinical populations with MDD. The majority of available studies are either observational, short in duration, or conducted on non-clinical populations, thus limiting the ability to reach conclusions on any correlations or generalisations regarding patients with a diagnosed mood disorder. IF protocols were quite varied between studies, be it in fasting duration, the eating window, calorie consumption, or length of intervention. The heterogeneity of this study's methodology complicates any attempts at direct comparisons between studies nor any attempts at determining the most optimal fasting regiment for mental health outcomes. Moreover, nutritional statuses were rarely assessed comprehensively. Most of the studies did not sufficiently evaluate micronutrient consumption, appetite-related hormones, nor potential risks such as malnutrition, fatigue, or worsening of any eating disorders. These are important gaps considering an IF intervention has metabolic consequences that can affect individuals with MDD differently¹⁴⁻¹⁶.

Despite the limitations, IF still has a potential as an additional (adjuvant) therapeutic intervention to treat MDD, particularly for patients with a low cognitive-affective subscore in patients that had previously responded poorly to standard antidepressive therapy. Current evidence shows that modulating energy metabolism, ketone availability, inflammatory pathways, and neuroplasticity mechanisms can complement pharmacological and psychotherapeutic approaches. However, IF cannot be considered as a singular therapy for MDD. Its implementation in a clinical setting should be based on the individual and should be integrated in a multidisciplinary treatment plan. Considering that IF is a diet-based intervention, supervision by competent healthcare workers including psychiatrists, nutritionists, and dieticians is recommended to ensure nutritional goals, minimise side effects, and identify contraindications such as

eating disorders, severe metabolic diseases, and frailty conditions^{9,15,16}.

From a clinical perspective, future research must prioritise long-term RCTs with a sufficient design, a standardised IF protocol, close supervision of fasting adherence, comprehensive monitoring of nutritional status, and a clinically relevant psychiatric outcome. Moreover, stratification based on symptom severity, diagnosis, sex, and metabolic status can help to identify patient groups that can benefit the most from IF-based intervention. Stronger scientific evidence and interdisciplinary collaboration are the main prerequisite before IF can be recommended as a routine clinical practice for MDD. Therefore, future research should directly compare different IF protocols to determine their relative effectiveness for the brain, to explore optimal durations for eating windows, and to investigate potential risks and side effects that may arise. These measures are important to develop targeted dietary interventions for the purpose of supporting cognitive health and mental wellbeing in individuals with MDD.

CONCLUSION

Several studies show a positive impact from intermittent fasting on alleviating the symptoms of major depressive disorder. This is based on several biological mechanisms including metabolic responses and an increased expression of neurotrophic factors such as BDNF that is correlated with an increased serotonin concentration, the circadian rhythm, the HPA axis, the regulation of the gut-brain axis. It can be concluded that intermittent fasting has the potential to be an additional (adjuvant) therapeutic option to alleviate mental disorders, in particular for major depressive disorder. Future research should assess what types of intermittent fasting can best be adopted as an adjuvant therapeutic option for major depressive disorder.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. American psychiatric association, Fifth Edition (DSM-5) & DSM-5-TR. American Psychiatric Publishing; 2022.
2. Szücs A, van der Lubbe SC, de la Torre JA, Valderas JM, Hay SI, Bisignano C, Morgan BW, Acharya S, Adnani QE, Apostol GL, Aslam MS. The epidemiology and burden of ten mental disorders in countries of the Association of Southeast Asian Nations (ASEAN), 1990–2021: findings from the Global Burden of Disease Study 2021. *The Lancet Public Health*. vol. 10, no. 6, pp. e480–e491, May 2025, doi: [https://doi.org/10.1016/S2468-2667\(25\)00098-2](https://doi.org/10.1016/S2468-2667(25)00098-2).
3. S. Sharifi, F. Rostami, Kimia Babaei Khorzoughi, and M. Rahmati, “Effect of time-restricted eating and intermittent fasting on cognitive function and mental health in older adults: A systematic review,” *Preventive medicine reports*, vol. 42, pp. 102757–102757, Jun. 2024, doi: <https://doi.org/10.1016/j.pmedr.2024.102757>.
4. E. Berthelot, D. Etchecopar-Etchart, D. Thellier, C. Lancon, L. Boyer, and G. Fond, “Fasting Interventions for Stress, Anxiety and Depressive Symptoms: a Systematic Review and Meta-Analysis,” *Nutrients*, vol. 13, no. 11, p. 3947, Nov. 2021, doi: <https://doi.org/10.3390/nu13113947>.
5. L. Murta, D. Seixas, L. Harada, Rodolfo Furlan Damiano, and M. V. Zanetti, “Intermittent Fasting as a Potential Therapeutic Instrument for Major Depression Disorder: A Systematic Review of Clinical and Preclinical Studies,” *International Journal of Molecular Sciences*, vol. 24, no. 21, pp. 15551–15551, Oct. 2023, doi: <https://doi.org/10.3390/ijms242115551>.
6. E. Mayor, “Neurotrophic effects of intermittent fasting, calorie restriction and exercise: a review and annotated

- bibliography,” *Frontiers in aging*, vol. 4, Jun. 2023, doi: <https://doi.org/10.3389/fragi.2023.1161814>.
7. Renjun Lv et al., “Intermittent fasting and neurodegenerative diseases: Molecular mechanisms and therapeutic potential,” *Metabolism*, pp. 156104–156104, Dec. 2024, doi: <https://doi.org/10.1016/j.metabol.2024.156104>.
 8. S. Rabiei, “The Association of Different Types of Intermittent Fasting with Mental Health: A Protocol for Systematic Review,” *International Journal of Preventive Medicine*, vol. 16, Jul. 2025, doi: https://doi.org/10.4103/ijpvm.ijpvm_312_24.
 9. B. Stapel et al., “Impact of fasting on stress systems and depressive symptoms in patients with major depressive disorder: a cross-sectional study,” *Scientific Reports*, vol. 12, no. 1, May 2022, doi: <https://doi.org/10.1038/s41598-022-11639-1>.
 10. S. Yousuf, A. Syed, and M. Yakoob Ahmedani, “To explore the association of Ramadan fasting with symptoms of depression, anxiety, and stress in people with diabetes,” *Diabetes Research and Clinical Practice*, p. 108545, Nov. 2020, doi: <https://doi.org/10.1016/j.diabres.2020.108545>.
 11. Y. Wang and R. Wu, “The Effect of Fasting on Human Metabolism and Psychological Health,” *Disease Markers*, vol. 2022, no. 1, pp. 1–7, Jan. 2022, doi: <https://doi.org/10.1155/2022/5653739>.
 12. Z. Zhao, W. Geng, Y. Gao, Y. Liu, S. Nie, and Q. Yin, “Effects of intermittent fasting on brain health via the gut–brain axis,” *Frontiers in Nutrition*, vol. 12, Nov. 2025, doi: <https://doi.org/10.3389/fnut.2025.1696733>.
 13. J. Gudden, A. Arias Vasquez, and M. Bloemendaal, “The Effects of Intermittent Fasting on Brain and Cognitive Function,” *Nutrients*, vol. 13, no. 9, p. 3166, Sep. 2021, doi: <https://doi.org/10.3390/nu13093166>.
 14. A. Chaix, E. N. C. Manoogian, G. C. Melkani, and S. Panda, “Time-Restricted Eating to Prevent and Manage Chronic Metabolic Diseases,” *Annual Review of Nutrition*, vol. 39, no. 1, pp. 291–315, Aug. 2019, doi: <https://doi.org/10.1146/annurev-nutr-082018-124320>.
 15. R. de Cabo and M. P. Mattson, “Effects of Intermittent Fasting on Health, Aging, and Disease,” *New England Journal of Medicine*, vol. 381, no. 26, pp. 2541–2551, Dec. 2019, doi: <https://doi.org/10.1056/nejmra1905136>.
 16. O. Patsalos, J. Keeler, U. Schmidt, B. W. J. H. Penninx, A. H. Young, and H. Himmerich, “Diet, Obesity, and Depression: A Systematic Review,” *Journal of Personalized Medicine*, vol. 11, no. 3, Mar. 2021, doi: <https://doi.org/10.3390/jpm11030176>.