Effects of brown rice bran on appetite and depression in metabolic syndrome: A secondary analysis of an open label randomized controlled trial

Marjan Mahdavi-Roshan[1#], Fatemeh Dashti[2#], Ehsan Zamani[3], Zeinab Ghorbani[1*], Arsalan Salari[4], Parham Porteghali[4], Zahra Ahmadnia[4]

[1]Department of Clinical Nutrition, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[2]Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran.

[3]Department of Pharmacology and Toxicology, School of Pharmacy, Guilan University of Medical Sciences, Rasht, Iran.

[4]School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.

*__Corresponding author:__ Zeinab Ghorbani, Ph.D. Assistant Professor of Nutrition Department of Clinical Nutrition, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran. Address: Guilan University of Medical Sciences' Headquarters, Parastar St., Rasht, Iran. Postcode: 41937-1311 TEL: 013-33345308 FAX: 013-33345308 z.ghorbani.h@gmail.com *zeinab.ghorbani@gums.ac.ir*

[#]Joint first authors.

Short title: BRBP in Diet: Effects on Ghrelin, Appetite, & Mood.

This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI
10.1017/S0007114525105540
The British Journal of Nutrition is published by Cambridge University Press on behalf of The Nutrition Society

Abstract

Although metabolic syndrome (MetSyn) patients are frequently reported to experience alterations in ghrelin levels, appetite regulation, and mood, these issues have been largely overlooked. Thus, the present RCT examined the effects of incorporating brown rice bran powder (BRBP) into a standard diet on ghrelin levels, appetite control, depression, insulin resistance, and atherogenicity indices. This secondary analysis used data from our 8-week RCT involving 43 MetSyn patients, with 19 on a standard diet and 24 receiving an additional 15 g/d of BRBP. Serum ghrelin levels were measured using an ELISA kit, and seven atherosclerosis-related indicators were assessed before and after the intervention. Appetite rating and depression status were evaluated using a four-component visual analogue scale (VAS) and the Beck Depression Inventory (BDI) questionnaires. The ANCOVA-model adjusted for baseline values (and BMI for ghrelin) indicated that patients receiving BRBP plus the standard diet experienced significant increases in ghrelin levels and feelings of satiety and fullness compared to those on the standard diet alone (P-value<0.008; effect sizes (ES) of 0.95, 1.14, and 1.34, respectively). BRBP intake led to significant reductions in AC, CRI-II, CHOLINDEX, METS-IR, BDI scores, and hunger sensations (P-value≤0.026; ES of -0.94, -0.96, -0.81, -1.74, -0.98, and -0.71, respectively) compared to the standard diet alone. Overall, this secondary analysis of the RCT supports the efficacy of BRBP administration in enhancing ghrelin levels while reducing appetite-related indices, depression scores, as well as markers of atherogenicity and insulin resistance. Nevertheless, given the study's limitations, namely small sample size and lack of a placebo, further research is needed.

Keywords: Insulin Resistance, Atherosclerosis, Standard diet, Oryza, Ghrelin.

Abbreviations

Metabolic syndrome (MetSyn), randomized controlled trial (RCT), brown rice bran powder (BRBP), body mass index (BMI), fasting blood sugar (FBS), enzymatic-colorimetric (CPO-POD), total cholesterol (TC), triglyceride (TG), Low-density lipoprotein-cholesterol (LDL-C), High-density lipoprotein-cholesterol (HDL-C), Atherogenic coefficient (AC), Castelli risk index-II (CRI-II), Triglyceride glucose (TyG) index, Atherogenic index of plasma (AIP), Lipoprotein combine index (LCI), Cholesterol index (CHOLINDEX), Metabolic score for insulin resistance (METS−IR), Visual Analogue Scales (VAS), Beck Depression Inventory (BDI), Analysis of covariance (ANCOVA), standard deviation (SD), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Peptide YY (PYY), Glucagon-Like Peptide-1 (GLP-1), short chain fatty acid (SCFA), 5-Hydroxyindoleacetic acid/5-Hydroxytryptamine (5-HIAA/5-HT), hypothalamic–pituitary–adrenal (HPA)glucose transporters-4 (GLUT-4), glucose transporters-5 (GLUT-5).

Introduction

Metabolic syndrome (MetSyn) is not defined as a sole disease; however, it is characterized throughout the co-occurrence of at least three of following risk factors: abdominal obesity, hyperglycaemia, insulin resistance , hypertension, and dyslipidaemia [1; 2; 3]. MetSyn is a certain public health challenge, and its rapid increase in regions like the Middle East underscores the need for effective nutritional and lifestyle interventions [1].

Beyond its well-established cardiometabolic complications, MetSyn is increasingly linked to less-recognized comorbidities, particularly appetite dysregulation and mood disorders. A key hormonal player in this relationship is ghrelin, the primary orexigenic hormone, acting as a central signal of energy deficit to the brain. A consistent finding in the literature is that metabolically unhealthy obese individuals and MetSyn patients might exert lower concentration of ghrelin, as compared with healthy subjects. The precise mechanism behind the reduced ghrelin levels' involvement in metabolic disturbances, though still requires further investigation [4; 5; 6; 7; 8; 9; 10; 11; 12]. Current research suggests that ghrelin-producing cells have a system closely tied to insulin and glucose levels in the blood, implying that insulin resistance and high blood sugar may suppress the release of ghrelin. This suppressed ghrelin concentration is proposed to be paradoxically associated with worse metabolic parameters. Dysregulation of ghrelin is also thought to contribute to aberrant appetite signalling, undermining dietary adherence and weight management efforts [8; 9; 10; 11; 12; 13; 14]. Recent evidence further illuminates ghrelin's role beyond appetite, suggesting a protective function against chronic stress and depression. Higher ghrelin levels have been correlated with a lower risk of metabolic problems linked to chronic stress and depression, highlighting its possible therapeutic benefits in mitigating depression-like symptoms caused by chronic stress as well as metabolic disorders [7; 15; 16]. This is critically relevant given the established bidirectional relationship between MetSyn and depression, which is thought to be mediated by shared pathways such as chronic inflammation, disruption of hypothalamic-pituitary-adrenal axis (HPA) and the imbalance of hormones, including ghrelin. Consequently, a therapeutic strategy that modulates ghrelin could simultaneously address metabolic dysregulation, appetite control, and depressive symptoms in MetSyn [17; 18; 19; 20; 21].

Dietary composition is a potent modulator of postprandial ghrelin response [12; 22; 23]. Emerging research indicates that certain dietary factors, with fiber being particularly noteworthy, appear to

markedly influence ghrelin levels and related pathways that affect appetite regulation and depressive symptoms, though findings remain nuanced [12; 22; 23; 24]. In this context, brown rice bran as a nutrient-dense functional food rich in bioactive compounds comprised of vitamin E (tocotrienols and tocopherols), isoflavones, beta-carotene, anthocyanins, γ-oryzanol, polyphenols, and dietary fiber, presents a promising dietary intervention. However, a critical gap exists in the evidence. While individual components are studied, the specific impact of brown rice bran powder (BRBP) on ghrelin physiology, appetite perception, and depression scores in a MetSyn population has not been rigorously investigated through a randomized controlled trial (RCT) design [25; 26; 27; 28; 29; 30; 31].

Therefore, utilizing data from our previous RCT [31], this secondary analysis aimed to determine the efficacy of an 8-week supplementation with 15 g/d of BRBP within a standard diet to modulate ghrelin levels, appetite control, depression, atherogenic indices, and insulin resistance surrogate markers in MetSyn patients, compared to a standard diet alone. We hypothesized that BRBP supplementation would significantly enhance ghrelin levels, improve satiety, reduce depression scores and enhance atherogenicity, and insulin resistance compared to a standard diet alone.

Method

Study design

The current trial is a secondary analysis of a single-centre, controlled, open-label, randomized trial investigating the effects of daily intake of BRBP (15 g) with a standard diet for 8 weeks in adults (male and female aged between 20 and 70 years) with MetSyn. The research design and data collection methods have been detailed in another source [31]. In summary, between April 2022 and June 2023, we engaged a total of fifty individuals diagnosed with MetSyn, sourced from the cardiology outpatient clinic at Dr. Heshmat Hospital in Rasht. The following factors were considered as inclusion criteria: patients who had MetSyn (≥3 parameters of MetSyn, such as hypertriglyceridemia (≥150 mg/dL), low levels of high-density lipoprotein-cholesterol (HDL-C) (<50 mg/dL in women; <40 mg/dL in men), hypertension (systolic ≥130 and/or diastolic ≥85 mm Hg), impaired fasting glucose (>100 mg/dL), and central adiposity (<102 cm in men; <88 cm in women) or intake of medicine for each parameter). Additionally, subjects with a medical

history of urolithiasis, gastrointestinal disorders, kidney diseases, cholelithiasis, autoimmune disorders, and kidney diseases; those who consumed alcohol; or individuals with a history of drug abuse or consuming supplements (fiber, omega-3, antioxidants, and vitamins and minerals), which could affect the outcomes of the intervention, as well as those who changed their treatment during the intervention or did not intend to follow the trials' instructions due to the taste of the powder or any personal reason, were also excluded from the intervention.

Based on age groups (20 to 45 years and 45 to 70 years), subjects were randomly assigned to either a standard diet group or BRBP with standard diet group using a computer-based stratified blocked randomization method, with a block size of 4.

Approval for this research was granted by the Institutional Review Board of Research Affairs at Guilan University of Medical Sciences (GUMS), which thoroughly scrutinized and endorsed the study under research number = 71213; 3734). The GUMS Ethics Committee further validated both the design and methodological procedures of the study, assigning the ethics code number IR.GUMS.REC.1400.388. Committed to ethical standards, the research adhered to the guidelines articulated in the Declaration of Helsinki (2013), ensuring that all participants signed and dated informed consent documents before any research procedures began; the trial protocol was also documented in the clinical trial registration system (IRCT registration number: IRCT20180205038626N11, Registration date: 2021-11-25; URL: https://en.irct.ir/trial/38346).

Intervention

As detailed in our previous report [31], at the beginning and end of the study period, each participant underwent a detailed interview conducted by a registered dietitian from the research team. These interviews were designed to collect comprehensive dietary intake data using the 24-hour dietary recall method. Based on the initial assessments, individualized diets were formulated to align with each participant's typical eating habits and personal preferences. Energy requirements and macronutrient distributions were calculated in accordance with the 2010 USDA Dietary Guidelines for Americans [32], resulting in a standard dietary composition of 55% carbohydrates, 30% fat, and 15% protein.

Participants were divided into two groups. The control group followed only the standard diet while the intervention group was instructed to incorporate 15 grams of brown rice bran

(approximately one tablespoon in powder form) into their daily intake alongside the standard diet. All individuals diagnosed with MetSyn continued to receive routine medical care and any prescribed medications throughout the study. None of the participants in either study group were prescribed antidepressant or antipsychotic medications before or during the trial period.

The BRBP used in the trial was supplied by Giltaz Company with no role in the study's design, conduct, analysis, or interpretation. Its nutritional and phytochemical composition was analysed using validated food-analysis techniques. High-performance liquid chromatography (HPLC), performed on an Agilent 1100 system, was used to measure total sugars, vitamin content, and γ-oryzanol. The contents of insoluble and soluble fiber were determined using enzymatic-gravimetric methods. Fat content was assessed via the Soxhlet extraction technique, and protein levels were measured using the Kjeldahl method. All laboratory analyses were conducted at Viromed Laboratory in Rasht, Iran. The nutrient profile of BRBP per 100 grams included 20.88 g of protein, 17.3 g of fat, 8.33 g of total sugars, 20.4 g of insoluble fiber, and 2.3 g of soluble fiber. It also contained 7.1 mg of vitamin E, 4.8 mg of thiamin (B1), 30.2 mg of niacin (B3), 6.17 mg of pantothenic acid (B5), 1.8 mg of pyridoxine (B6), and 57 mg of γ-oryzanol. Safety evaluations confirmed that the BRBP was free from detectable levels of harmful mycotoxins, including aflatoxins B1, B2, G1, G2, ochratoxin A, zearalenone, and deoxynivalenol. Microbiological analysis revealed that the total count of molds and microorganisms was less than 10 colony-forming units per gram (CFU/g), and no traces of Escherichia coli or sulfite-reducing Clostridium were found, ensuring the product’s safety for consumption.

Demographic, and Anthropometrics measurements

Upon collecting the sociodemographic data of the recruited participants, which encompassed age and job status, a standard stadiometer and the Seca 755 medical scale with a precision of 0.1 cm and 0.5 kg, respectively, were utilized to measure height and weight in pre- and post-intervention. A computing of BMI was done using the formula weight (kg) divided by the square of height (m^2) [31].

Biological sample collection and analysis

For measuring serum levels of ghrelin, fasting blood sugar (FBS), and lipid profile, an eight mL sample of venous blood in fasting conditions was collected from subjects at pre- and post-

research periods. Sodium citrate was incorporated into the sterile containers to protect samples from coagulation. Plasma was separated from serum aliquots through centrifugation, and then both of them were stored in a -70°C freezer. The method of enzymatic-colorimetric (CPO-POD) was performed to assess the serum levels of total cholesterol (TC), HDL-C, and FBS using cholesterol oxidase, cholesterol esterase, and glucose oxidase, respectively, commercial kits (MAN Co., Tehran, Iran), and an auto-analyzer (Hitachi 917/Olympus 640). In addition, low-density lipoprotein-cholesterol (LDL-C) was computed via the Friedewald formula. The Bionic Corporation commercial kit and glycerol phosphate oxidase were also used to assess the serum concentration of triglyceride (TG) in the same way. To assess the serum level of total fasting ghrelin, a double-antibody sandwich enzyme-linked immunosorbent was applied using the Human Ghrelin ELISA kit (Intra-Assay: CV < 10%; Inter-Assay: CV < 12%; Crystal Day kit, Cat No: E3091Hu, (Bioassay Technology Co)).

Appetite assessment based on Visual Analogue Scales (VAS)

Individuals with MetSyn were asked to fill out a four-component visual analogue scale (VAS) questionnaire to evaluate their appetite rating. Various parameters were assessed in the VAS questionnaire, including desire to eat, feeling of fullness, satiety, and hunger. Each single VAS scale was a 100 mm horizontal line with labels anchoring at both ends, elucidating the lowest (e.g., for fullness, “Not at all having a feeling of fullness”) and highest (e.g., for fullness, “Extremely fullness”) rating of each parameter [33; 34; 35]. The investigators completed the VAS questionnaire at pre- and post-intervention. It should be mentioned that subjects did not have any information about their prior scores obtained from VAS questionnaire.

Beck Depression Inventory

The Beck Depression Inventory (BDI) is a validated questionnaire to examine the status of depression. Such a questionnaire is self-reported and consists of 21 multiple-choice questions. The answer to each question has four categories, ranging from 0 (no symptoms of depression) to 3 (severe symptoms). Therefore, the total of all responses is between 0 and 63. For each single question, participants have to select the best options which represent their situation during the last eight weeks [36; 37].

Definition of the atherosclerosis related indices and insulin resistance surrogate markers

The atherogenic status indices were estimated on the basis of these calculations:

- Atherogenic coefficient (AC) $= \frac{\text{total cholesterol}\left(\frac{\text{mmol}}{\text{L}}\right) - \text{HDL}-\text{C}\left(\frac{\text{mmol}}{\text{L}}\right)}{\text{HDL}-\text{C}\left(\frac{\text{mmol}}{\text{L}}\right)}$ [38].
- Castelli risk index $-$ II (CRI $-$ II) $= \frac{\text{LDL}-\text{C}\left(\frac{\text{mmol}}{\text{L}}\right)}{\text{HDL}-\text{C}\left(\frac{\text{mmol}}{\text{L}}\right)}$ [38; 39].
- Triglyceride glucose (TyG) index $= Ln\left(\frac{\text{fasting triglycerides}\left(\frac{\text{mg}}{\text{dL}}\right)\times \text{fasting glucose}\left(\frac{\text{mg}}{\text{dL}}\right)}{2}\right)$ [40].
- Atherogenic index of plasma (AIP) $= Log_{10}\left(\frac{\text{triglycerides}\left(\frac{\text{mmol}}{\text{L}}\right)}{\text{HDL}-\text{C}\left(\frac{\text{mmol}}{\text{L}}\right)}\right)$ [38; 39; 41].
- Lipoprotein combine index (LCI) $= \frac{\text{total cholesterol}\left(\frac{\text{mmol}}{\text{L}}\right)\times \text{triglycerides}\left(\frac{\text{mmol}}{\text{L}}\right)\times \text{LDL}-\text{C}\left(\frac{\text{mmol}}{\text{L}}\right)}{\text{HDL}-\text{C}\left(\frac{\text{mmol}}{\text{L}}\right)}$ [39; 42].
- Cholesterol index (CHOLINDEX) $= \text{LDL}-\text{C}\left(\frac{\text{mmol}}{\text{L}}\right) - \text{HDL}-\text{C}\left(\frac{\text{mmol}}{\text{L}}\right)$

  (All patients had triglycerides < 400 mg/dL) [43; 44].
- Metabolic score for insulin resistance index (METS $-$ IR) $=$

  $\frac{\text{Ln}\left(\left(2\times\text{fasting glucose}\left(\frac{\text{mg}}{\text{dL}}\right)\right)+\text{fasting triglycerides}\left(\frac{\text{mg}}{\text{dL}}\right)\right)\times\text{BMI}}{\text{Ln}\left(\text{HDL}-\text{C}\left(\frac{\text{mg}}{\text{dL}}\right)\right)}$ [45].

Sample size calculation and Statistical methods

As described in our earlier report [31], the estimated sample size for the present trial was derived from the formula described below, taking Ito et al.[46] as a reference, and targeted 25 participants per group, accounting for an expected dropout of approximately 15%. A statistical power of 80% was selected with the aim of achieving a minimum reduction of 27 mg/dL in total cholesterol. The significance level was set at $\alpha = 0.05$ and the complement of power (β) at 0.20, with the

group-specific standard deviations SD1 = 29.0 and SD2 = 33.5, yielding a detectable difference d = 27.

$$N = 2 \times \left((Z_{1-(\alpha/2)} + Z_{1-\beta})^2 \times (SD_1^2 + SD_2^2)\right) / (\bar{X}_1 - \bar{X}_2)^2$$

Shapiro-Wilk test was applied to evaluate the normality of data. Then, the comparison of between-group differences in quantitative and categorical variables was done using chi-square and independent-sample t-tests, respectively. Analysis of covariance (ANCOVA) controlling for the baseline values (and BMI changes in case of analysing changes in ghrelin) was then conducted to explore the impacts of BRBP plus standard diet in comparison with standard diet alone on ghrelin levels, atherogenicity indices and insulin resistance surrogate markers as well as appetite and depression scores. Accordingly, the adjusted means and 95% confidence intervals (95% CIs) were demonstrated in the table. The test level for statistical significance was considered as P-value less than 0.05.

Moreover, to assess the effect size for each outcome, denoted as Cohen's d [(44)], the mean difference post-intervention was calculated and divided by the overall standard deviation. This calculation yields a standardized measure that reflects the difference between the BRBP plus standard diet group and standard diet group, allowing for a more comprehensive evaluation of the intervention's impact. The classification of effect sizes based on Cohen's d values [(44)] includes trivial for d < 0.2, mild for 0.20 - 0.49, moderate for 0.50 - 0.79, and large for d > 0.80. Statistical analysis was performed using STATA version 16 (StataCorp LLC, College Station, TX, USA).

Results

Sample Description

Overall, 43 patients with MetSyn were analysed in the current investigation, of which 24 were treated with BRBP plus standard diet (intervention group) and 19 only received standard diet plan (Figure 1). Reasons for withdrawal included personal circumstances (one from each group) and modifications to their therapeutic regimens (such as changes in prescribed medications (n=4), or using fiber supplement (n=1)) which affected five individuals in the control group. Detailed attrition data are illustrated in our previous report [(31)]. Approximately half of the

participants in both groups were female. The age was homogeneously distributed between two groups and on average was about 49 and 52 years, among control and intervention groups, respectively. The means of BMI of patients in the BRBP plus standard diet and standard diet groups were about 32.19 and 32.48 kg/m^2, respectively, with no considerable differences between groups. The mean serum levels of metabolic factors at the enrolment were also equally distributed between the two studied groups, except those patients in the intervention group displayed significantly greater TC concentrations than the control group subjects (P-value = 0.009) (Table 1).

Effects of intervention on serum ghrelin and appetite and depression scores

At study enrolment, no significant differences were observed between groups in the serum levels of ghrelin, scores of feeling hunger, fullness, and satiety sensations, desire to eat, or depression. The detailed findings of the present RCT regarding anthropometric indices including BMI and WC have been published previously [(31)]. Figure 2 highlights the effectiveness of the intervention in reducing BMI relative to the control group. There was a significantly greater reduction in the mean (SD) of BMI changes in the intervention group (-1.45 (1.24)) than in the controls (0.19 (1.29)) (Figure 2). After the 8-week trial, it was found that supplementing the standard diet with 15 g/d of BRBP significantly elevated serum ghrelin levels, with a large effect size compared with the standard diet alone (baseline and BMI-adjusted mean (SD): 0.83 (0.18) vs. 0.65 (0.20); effect size: 0.95 (0.30 – 1.58); P-value < 0.008, using ANCOVA) (Table 2).

In the same way, it was shown that compared to the subjects who followed a standard diet the appetite level of the patients who additionally consumed 15g/d of BRBP significantly improved, as reflected by moderately lower score of hunger feeling, and largely higher scores of satiety and fullness sensations (hunger baseline-adjusted mean (SD): 6.33 (1.47) vs. 7.38 (1.48); effect size: -0.71 (-1.33 – -0.08); satiety baseline-adjusted mean (SD): 7.15 (1.67) vs. 5.23 (1.68); effect size: 1.14 (0.49 – 1.79); fullness baseline-adjusted mean (SD): 6.65 (1.16) vs. 5.08 (1.17); effect size: 1.34 (0.67 – 2.00); P-value ≤ 0.026, using ANCOVA). However, no meaningful differences were observed in the scores of desire to eat at the study endpoint (Table 2).

Analyzing the BRBP effects on depression through comparing the BDI scores of the studied groups revealed that the mean BDI score was considerably and largely lower in the intervention

group, as compared to the controls, after the 8-week trial (baseline-adjusted mean (SD): 9.75 (4.07) vs. 13.74 (4.07); effect size: -0.98 (-1.61 – -0.34); P-value = 0.003, using ANCOVA) (Table 2).

Effects of intervention on novel atherogenicity and insulin resistance surrogate indices

The detailed findings of the present RCT regarding serum lipid and glycaemic parameters have been reported previously [31]. Table 3 presents post-hoc analysis of changes in atherogenicity indices in patients with MetSyn before and after receiving 15 g/d of BRBP while adhering to the standard diet or following only a standard diet plan in this 8-week RCT. There were no significant differences at the baseline levels of CRI-II, TyG index, AIP, CHOLINDEX, and METS-IR between the subjects in both BRBP plus standard diet and control groups. While, in the beginning, the patients in the intervention group were shown to have significantly greater mean values of AC, and LCI (P-value < 0.05) (Table 3).

At 8th week, the enhancements in the majority of indicators of atherogenicity and insulin resistance were revealed to be more pronounced among the patients who consumed BRBP plus standard diet in comparison with those who only received a standard diet plan. As such, following controlling for baseline levels of the indices in ANCOVA models, these patients demonstrated significantly lower AC, CRI-II, CHOLINDEX, and METS-IR levels with large effect sizes than the subjects in the control arm (AC baseline-adjusted mean (SD): 2.54 (0.98) vs. 3.48 (0.99), effect size: -0.94 (-1.57 - -0.30); CRI-II baseline-adjusted mean (SD): 1.69 (0.67) vs. 2.34 (0.68), effect size: -0.96 (-1.60 - -0.32); CHOLINDEX baseline-adjusted mean (SD): 0.75 (0.72) vs. 1.34 (0.73), effect size: -0.81 (-1.43 - -0.18); METS-IR baseline-adjusted mean (SD): 49.28 (2.98) vs. 54.49 (2.99), effect size: -1.74 (-2.45 - -1.03)) (P-value ≤ 0.013) (Table 3). In addition, marginally significant differences were noted in TyG index, and LCI levels between the two studied groups following an 8-week intervention. Patients in the BRBP within standard diet group had a tendency of having moderately lower levels compared to the control group with moderate effect sizes than the subjects in the control arm (TyG baseline-adjusted mean (SD): 9.10 (0.46) vs. 9.35 (0.47), effect size: -0.54 (-1.15 - 0.08); LCI baseline-adjusted mean (SD): 14.94 (18.93) vs. 25.94 (19.04), effect size: -0.58 (-1.19 - 0.04)) (P-value < 0.1) (Table 3).

Discussion

The findings of this secondary analysis demonstrate that an 8-week supplementation with 15 g/d of BRBP within a standard diet elicited a multifaceted beneficial response in individuals with MetSyn. Notably, we observed a significant increase in serum ghrelin levels, concomitant with improved subjective appetite ratings (reduced hunger, increased satiety and fullness), reduced depression scores, and improved atherogenic and insulin resistance indices.

The most intriguing finding of our study is the significant increase in total ghrelin levels following BRBP supplementation, which appears counterintuitive given its role as a hunger-stimulating hormone. However, this finding seems to partly align with the established physiology of ghrelin as a counter-regulatory hormone sensitive to energy balance [4; 5; 6; 7; 8; 9; 10; 11; 12; 47; 48; 49]. Partly similar to our findings, Kim, et al (2024) [49], in a recent double-blind, placebo-controlled, crossover trial emphasizes that specific fibers from Barley, rich in the soluble fiber β-glucan significantly improved subjective appetite measures using the VAS scores, lowered hunger and increased satiety and fullness scores compared to a placebo after 60 min; however, these findings did not correspond with significant changes in the physiological markers ghrelin and PYY [49]. Interestingly, while the BDF group had higher absolute ghrelin levels 60 min after glucose loading (807.5 ± 48.7 pg/mL vs. 713.8 ± 40.4 pg/mL in the placebo group), the hormone's dynamic pattern of postprandial decrease was maintained. The authors attributed the enhanced satiety not to ghrelin suppression alone but to a synergistic increase in anorexigenic hormones like PYY. This highlights that the net effect on appetite is determined by the balance between orexigenic and anorexigenic signals, and fiber may favourably shift this balance [49]. Our results also align with another study reporting intake of modified oat bran led to a considerable mitigation in the serum concentration of ghrelin among twenty healthy individuals [48]. However, Wang et al., in 2023, indicated that a diet with 20% wheat bran in sows could decrease the levels of ghrelin [50]. Besides, in contrast to the present findings, another RCT conducted by Triffoni-Melo in 2023 on obese women on a short-term, high-fiber, calorie-restricted diet (1000 kcal/day) showed that such a diet has suppressed postprandial (after 60 min) acylated ghrelin, but not total ghrelin [47]. However, it should be noted that this trial indicated the significant decrease in postprandial acylated ghrelin, and not total fasting ghrelin levels [47]. There are also a number of studies that failed to show significant changes in ghrelin levels in 34

Filipino subjects following consumption of brown rice in a trial study conducted by Golloso-Gubat et al. in 2016 [51]. Wolever et al. in 2020 also reported that increasing the viscosity of oat β-Glucan in a breakfast failed to exert a promising effect on the ghrelin concentration [52]. Inconsistencies in the standardization of ghrelin level measurements, such as the timing of sample collection, collection methods, follow-up periods, sample storage, and the radioimmunoassay employed could affect the precision and reproducibility of the findings. Besides, although ghrelin hormone has two forms including des-acylated ghrelin and acylated ghrelin [6], to the best of our knowledge, except for the study by Triffoni-Melo et al [47], none of the others specifically focus on measuring the active form of ghrelin; instead, total ghrelin levels are typically assessed. Future research must measure acyl-ghrelin to clarify its specific dynamics in response to BRBP.

It should be noted that lower serum concentration of ghrelin has been linked to the progression of hyperglycaemia, insulin resistance, diabetes mellitus, and hypertension, particularly in obese populations [7; 9; 53; 54; 55; 56]. Although there are several hypotheses have been explored in the recent studies, none of them report the accurate mechanism regarding reduction of ghrelin levels in patients with metabolic disturbances. The most recent affirmed hypothesis suggests that hyperinsulinemia and hyperglycaemia may inhibit the secretion of ghrelin. This relationship could contribute to the lower ghrelin levels observed in obese individuals and those who suffer from insulin resistance-associated metabolic disorders, particularly MetSyn [7; 9; 53; 54; 55; 56]. Interestingly, there is a complex inverse relationship between ghrelin and BMI. Ghrelin levels tend to be lower in individuals with obesity and higher in lean individuals, including those with anorexia nervosa, suggesting a counter-regulatory signal to prevent further weight gain in obesity [10; 11]. In our initial analysis of the same RCT [31], greater reductions in anthropometric measurements, specifically BMI and WC, were noted compared with the controls. These findings likely triggered a compensatory rise in ghrelin, an evolutionary adaptation to defend body weight and promote energy intake [49]. To account for this dynamic in our analyses, we controlled the ANCOVA models examining BRBP effects on serum ghrelin for changes in BMI over the trial. Hence, the observed increase in serum ghrelin levels following BRBP consumption also reflects adjustment for BMI changes.

It should be bear in mind that ghrelin secretion is not merely responsive to short-term fasting but also adapts to long-term changes in energy balance [47]. Hence, this compensatory mechanism is well-documented in weight-loss interventions, where elevated ghrelin poses a significant challenge to long-term weight maintenance by promoting hyperphagia and potential weight regain [47]. Crucially, our trial showed that, despite the rise in ghrelin, participants reported markedly improved appetite control. Alongside the ghrelin elevation, BRBP participants reported lower hunger and greater satiety and fullness than those following the standard diet (effect sizes: d = -0.71 for hunger, d = 1.14 for satiety, d = 1.34 for fullness). This pattern aligns with a countervailing influence of BRBP on perceived appetite despite ghrelin elevation. Supporting this, Golloso-Gubat et al. found that six weeks of brown rice consumption reduced feelings of hunger and increased satiety compared with white rice in healthy participants [51].

This discrepancy highlights the complex nature of appetite regulation, which involves not only circulating hormone levels but also neural pathways, sensory cues, and psychological factors. It suggests that the net effect on appetite is determined by the balance between orexigenic signals (e.g., ghrelin) and anorexigenic signals (e.g., Peptide YY (PYY), Glucagon-Like Peptide-1 (GLP-1),) [10; 11; 49]. Additional factors may contribute to subjective sensations of hunger and satiety independently of ghrelin and PYY, including individual variability in hormone sensitivity and postprandial metabolic responses, where some individuals experience satiety at lower hormone concentrations and others require higher levels to perceive similar effects [10; 11; 49].

We postulate that improving appetite sensation by BRBP in the current study may predominantly be attributed to a satiety-promoting properties of the bran layer of rice owning to slowing down the rate of gastric emptying and tending to prolong the process of nutrient absorption during the digestion. Moreover, short-chain fatty acids (SCFAs), resulted from the fiber fermentation of brown rice bran, could induce prolonged gastric emptying and elevate feelings of satiety [57; 58; 59; 60; 61; 62]. Moreover, brown rice bran may be able to stabilize the serum level of glucose and consequently inhibit the production of acyl-ghrelin, which influences the hypothalamus to stimulate hunger sensation [63; 64; 65]. However, acknowledging the subjective nature of appetite ratings, it remains unclear whether the rise in ghrelin levels reflects a normalization of dysregulated ghrelin dynamics in patients with MetSyn or supports the hypothesis that elevated ghrelin following weight loss may exacerbate difficulties in sustaining long-term weight loss,

thus contributing to the high failure rates commonly associated with dietary interventions aiming to reducing weight [6; 66]. Nonetheless, given the limited understanding of the impact of BRBP on ghrelin levels and appetite ratings, further research is necessary to elucidate this relationship in greater detail.

Additionally, considering the findings of the current intervention on depression status of the studied subjects, it was indicated that the patients who received BRBP in addition to the standard diet plan tended to have a largely lower BDI score after following an 8-week intervention compared to the patients who only followed a standard diet plan (large effect size: -0.98). A number of studies have also achieved similar results [67; 68]. An animal study highlighted that consumption of pre-germinated brown rice for 30 days accounted for a significant antidepressant effect in male mice through increasing the level of serotonin and reduction in the ratio of 5-Hydroxyindoleacetic acid / 5-Hydroxytryptamine (5-HIAA/5-HT) [67]. Such results were also confirmed in another in-vivo research for mice with chronic restraint stress-induced depression [68]. Moreover, brown rice bran is abundant in γ-oryzanol, omega-3 fatty acid and vitamin E, which are suggested to provide anti-depressive, antihypertensive and antioxidants effects. Thus, our current conclusion regarding the reduction of depressive symptoms may be explainable according to the antidepressant impacts of brown rice bran [69; 70]. With respect to the possible mechanism, brown rice bran may contribute to normalizing the hyperactivity of Hypothalamic–Pituitary–Adrenal (HPA) axis, reducing the expression of monoamine oxidase, sustaining the serum levels of monoamine, and alleviating the secretion of dopamine, norepinephrine, and serotonin [68]. Experimental studies additionally suggest that higher ghrelin levels, similar to when it is injected under the skin, may help reduce anxiety and depression. This increase in ghrelin, often together with calorie-restricted diets, might contribute to the currently observed antidepressant effects of BRBP [7; 15; 16].

With respect to the efficacy of BRBP on novel atherogenicity and insulin resistance indicators, the current findings showed that AC, CRI-II, CHOLINDEX, and METS-IR levels (indices primarily based on cholesterol or FBS ratios) most likely reduced following receiving 15 g/d of BRBP plus standard diet in comparison with the MetSyn participants who exclusively followed standard diet plan (large effect sizes: -0.94, -0.96 and -0.81, respectively). Regarding other parameters, including TyG index, and LCI, which appeared to mainly related to triglyceride

levels, the estimated effect sizes indicated a medium improving effect following consuming 15 g/d of BRBP plus standard diet compared to the standard diet alone (moderate effect sizes: -0.54, -0.53, and -0.58, respectively), though the between group comparisons demonstrated marginally significant differences (P-value<0.1). The comparatively modest changes in triglyceride-related indices, which align with our earlier findings [31], likely reflect the temporal sequence of improvements, wherein insulin resistance improves before triglyceride metabolism fully normalizes. Although to the best of our knowledge there is no similar trial in which the levels of atherogenicity and insulin resistance surrogate markers are investigated following BRBP supplementation, these results are at least partly in accordance with the available evidence indicating lipid-lowering impact of rice bran [46; 71; 72; 73; 74; 75; 76; 77]. It can be mentioned that administration of BRBP, as a functional food, with standard diet might exert a favourable effect on managing lipid profile and improve insulin resistance due to its high quality of nutraceutical components including vitamin E (tocotrienols and tocopherols), γ-oryzanol and fiber. Compelling evidence proposed a significant role of γ-oryzanol in ameliorating atherogenic status through various ways such as controlling the lipogenic enzyme activities and elevating the faecal excretion of bile acids and cholesterol. In addition, experimental investigations have suggested that brown rice bran contributed to the decrease of serum level of insulin and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) score, and augment sensitivity to insulin. Brown rice bran may also be able to stimulate the expression of glucose transporters-4 and 5 (GLUT-4 and GLUT-5) as well as ameliorate insulin receptor activity and insulin receptor substrate-1. Remarkably, SCFAs, generated from the fermentation of BRBP fiber by beneficial gut bacteria can influence the balance of lipids and glucose in the liver. Additionally, these SCFAs can serve as precursors for cholesterol, ultimately leading to a reduction in cholesterol synthesis. Impressively, studies suggest that ghrelin may be involved in promoting the breakdown of fats while simultaneously inhibiting insulin secretion. Consequently, in individuals with MetSyn who particularly exhibit signs of insulin resistance, higher levels of ghrelin might encourage a reduction in insulin production and facilitate greater fat breakdown. Accordingly, the observed result of rise in ghrelin levels following BRBP plus standard diet could also contribute to alleviating insulin resistance and improving insulin sensitivity [25; 26; 28; 29; 55; 78; 79; 80; 81].

Clinical relevance of the current findings

The findings from this 8-week study indicate that consuming 15 g/d of brown rice bran (approximately one tablespoon in powder form) within a standard dietary plan could be a promising therapeutic tool for the complementary management of MetSyn. Its ability to significantly enhance subjective appetite regulation (effectively decoupling ghrelin levels from hunger perception) might directly addresses a key barrier to dietary adherence. Furthermore, concurrent improvements in atherogenic risk profiles, insulin resistance surrogate markers, and depressive symptoms would position BRBP as a multi-targeted intervention capable of addressing several core facets of MetSyn simultaneously.

Future direction

According to the current findings, a high-fiber intervention such as BRBP hold promise for obesity and MetSyn management by increasing satiety even when ghrelin levels rise, a pattern that might often observed after weight loss and thought to complicate long-term weight maintenance. To build a robust evidence base for these effects, future research should address several key areas. First, extended, well-designed placebo-controlled trials (using matched bran-free powder) that include participants without MetSyn are needed to track both active (acylated) and inactive (des-acylated) ghrelin forms beyond the intervention period. Building on this, studies should adopt a multifaceted strategy including measuring a broad array of appetite-regulating hormones (e.g., GLP-1, leptin, PYY, GIP), evaluating potential improvements in central ghrelin sensitivity, and determining whether favourable appetite and ghrelin dynamics persist over the long term. Additionally, future work should investigate the microbiome's role in mediating these effects by examining fiber-driven shifts in gut microbial communities and SCFA production. Finally, broadening investigations to include populations without MetSyn will be essential to enhance the generalizability of the findings.

Strengths and limitations

This study has several notable strengths. To our knowledge, there is no similar trial aiming to assess the effects of BRBP administration on appetite and weight regulating pathways. In addition, a face-to-face interview for each single subject was performed by our study dietitian, and each participant received a customized standard diet. The focus on BRBP is particularly

relevant for the Iranian population, as the study was conducted in Guilan province (a major rice-producing region) making it an inexpensive and culturally pertinent dietary intervention.

However, the findings must be considered in light of several limitations. The open-label design, which lacked a placebo control, alongside the short 8-week intervention period, may constrain the interpretation of the results. Although we employed strategies to mitigate confounding, including randomization, dietary standardization, and ANCOVA models adjusted for baseline values and BMI (in case of serum ghrelin analysis), the potential for residual confounding persists including physical activity, smoking and medications effects. Additional limitations include the reliance on self-reported appetite and depression assessment data, which are subjective and susceptible to bias. Future studies would benefit from incorporating objective biomarkers. Finally, the hormonal analysis was restricted to ghrelin, omitting other critical appetite regulators like leptin, PYY, GLP-1, and GIP, which provides an incomplete metabolic picture. Consequently, these results should be interpreted with caution.

Conclusion

In summary, this secondary analysis reveals that an 8-week open label trial delivering 15 g/d BRBP within a conventional diet elicits a multifaceted beneficial response in individuals with MetSyn. The most intriguing finding is a significant increase in serum ghrelin levels, which occurred alongside markedly improved subjective appetite ratings (reduced hunger, increased satiety and fullness). Beyond appetite, BRBP supplementation yielded significant improvements in depression scores and key metabolic indices, including novel markers of atherogenicity (AC, CRI-II) and insulin resistance (METS-IR). These effects are likely mediated through BRBP's rich bioactive composition, including dietary fiber, γ-oryzanol, and vitamin E complexes, which may influence gut-brain axis signalling, metabolic function, and neuroregulation. Practically, BRBP emerges as an inexpensive, culturally appropriate, and effective functional food adjuvant to standard dietary therapy for MetSyn. It offers a promising strategy to improve metabolic health, enhance satiety, and support psychological well-being, thereby potentially improving long-term adherence to weight management plans. Nevertheless, given the study’s limitations, namely the small sample size and the absence of a placebo control, further research is needed to elucidate these effects in greater detail. Future research should prioritize longer-term, placebo-controlled trials that include a full panel of appetite hormones (including acylated ghrelin, leptin, PYY, and

GLP-1) and objective biomarkers to fully elucidate the mechanisms behind these compelling clinical benefits.

Declarations

Acknowledgements

The authors would like to thank the Giltaz Company which donated the powders with no conflict of interest. The donating company was not involved in study design, acquiring data, statistical analysis, results interpretation, or publication. None of the authors had any affiliation to this company. We also extend our gratitude to the patients who participated in the study as well as Ms. Nargeskhatoon Shoaibinobarian for her kind cooperation in baseline data collection.

Financial Support

This study was financially supported by Guilan University of medical sciences, Rasht, Iran (registered with research number = 71213; 3734).

Conflict of Interest

None of the authors have any conflict of interest to disclose.

Authorship

MMR and ZGh: Conceptualization, funding acquisition, methodology, project administration and supervision. ZGh and FD: Formal analysis, validation, visualization and writing original draft. MMR, EZ, AS, PP, ZA, ZGh, and FD: Methodology, investigation and resources. ZGh, MMR, FD, EZ, AS, PP, and ZA: Writing review, editing and approving the final draft.

References

1. Wang HH, Lee DK, Liu M *et al.* (2020) Novel insights into the pathogenesis and management of the metabolic syndrome. *Pediatric gastroenterology, hepatology & nutrition* **23**, 189.

2. Rader DJ (2007) Effect of insulin resistance, dyslipidemia, and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. *The American journal of medicine* **120**, S12-S18.

3. Huang PL (2009) A comprehensive definition for metabolic syndrome. *Disease models & mechanisms* **2**, 231-237.

4. Fahed G, Aoun L, Bou Zerdan M *et al.* (2022) Metabolic syndrome: updates on pathophysiology and management in 2021. *International journal of molecular sciences* **23**, 786.

5. Abulmeaty MMA, Aldisi D, Aljuraiban GS *et al.* (2022) Association of Gastric Myoelectrical Activity With Ghrelin, Gastrin, and Irisin in Adults With Metabolically Healthy and Unhealthy Obesity. *Front Physiol* **13**, 815026.

6. Makris MC, Alexandrou A, Papatsoutsos EG *et al.* (2017) Ghrelin and Obesity: Identifying Gaps and Dispelling Myths. A Reappraisal. *In vivo (Athens, Greece)* **31**, 1047-1050.

7. Kim S, Nam Y, Shin SJ *et al.* (2020) The potential roles of ghrelin in metabolic syndrome and secondary symptoms of Alzheimer's disease. *Frontiers in Neuroscience* **14**, 583097.

8. Ukkola O, Pöykkö SM, Antero Kesäniemi Y (2006) Low plasma ghrelin concentration is an indicator of the metabolic syndrome. *Annals of medicine* **38**, 274-279.

9. Jabbari M, Kheirouri S, Alizadeh M (2018) Decreased Serum Levels of Ghrelin and Brain-Derived Neurotrophic Factor in Premenopausal Women With Metabolic Syndrome. *Laboratory Medicine* **49**, 140-146.

10. Schaefer M, Kühnel A, Enge S (2024) Open-label placebos reduce weight in obesity: a randomized controlled trial. *Sci Rep* **14**, 21311.

11. Gajewska A, Strzelecki D, Gawlik-Kotelnicka O (2023) Ghrelin as a Biomarker of "Immunometabolic Depression" and Its Connection with Dysbiosis. *Nutrients* **15**.

12. Skoracka K, Hryhorowicz S, Schulz P *et al.* (2025) The role of leptin and ghrelin in the regulation of appetite in obesity. *Peptides* **186**, 171367.

13. Ukkola O, Pöykkö SM, Antero Kesäniemi Y (2006) Low plasma ghrelin concentration is an indicator of the metabolic syndrome. *Annals of medicine* **38**, 274-279.

14. Ukkola O, Pöykkö S, Päivänsalo M *et al.* (2008) Interactions between ghrelin, leptin and IGF-I affect metabolic syndrome and early atherosclerosis. *Annals of medicine* **40**, 465-473.

15. Lutter M, Sakata I, Osborne-Lawrence S *et al.* (2008) The orexigenic hormone ghrelin defends against depressive symptoms of chronic stress. *Nature neuroscience* **11**, 752-753.

16. Gajewska A, Strzelecki D (2023) Ghrelin as a Biomarker of "Immunometabolic Depression" and Its Connection with Dysbiosis. **15**.

17. Wang Q, Chair SY, Wong EM-L (2017) The effects of a lifestyle intervention program on physical outcomes, depression, and quality of life in adults with metabolic syndrome: a randomized clinical trial. *International journal of cardiology* **230**, 461-467.

18. Zhang M, Chen J, Yin Z *et al.* (2021) The association between depression and metabolic syndrome and its components: a bidirectional two-sample Mendelian randomization study. *Translational psychiatry* **11**, 633.

19. Pan A, Keum N, Okereke OI *et al.* (2012) Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes care* **35**, 1171-1180.

20. Zhou L-N, Ma X-C, Wang W (2024) Incidence and risk factors of depression in patients with metabolic syndrome. *World Journal of Psychiatry* **14**, 245.

21. Al-Khatib Y, Akhtar MA, Kanawati MA *et al.* (2022) Depression and metabolic syndrome: a narrative review. *Cureus* **14**.

22. Lutsey PL, Steffen LM, Stevens J (2008) Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. *Circulation* **117**, 754-761.

23. Andersen CJ, Fernandez ML (2013) Dietary strategies to reduce metabolic syndrome. *Reviews in Endocrine and Metabolic Disorders* **14**, 241-254.

24. St-Pierre DH, Rabasa-Lhoret R, Lavoie ME *et al.* (2009) Fiber intake predicts ghrelin levels in overweight and obese postmenopausal women. *European journal of endocrinology* **161**, 65-72.

25. Sarker M, Rahman M (2017) Dietary fiber and obesity management–a review. *Adv Obes Weight Manag Control* **7**, 00199.

26. Sapwarobol S, Saphyakhajorn W, Astina J (2021) Biological functions and activities of rice bran as a functional ingredient: A review. *Nutrition and metabolic insights* **14**, 11786388211058559.

27. Abd Razak DL, Abd Rashid NY, Jamaluddin A *et al.* (2015) Enhancement of phenolic acid content and antioxidant activity of rice bran fermented with Rhizopus oligosporus and Monascus purpureus. *Biocatalysis and Agricultural Biotechnology* **4**, 33-38.

28. Sivamaruthi BS, Kesika P, Chaiyasut C (2018) A comprehensive review on anti-diabetic property of rice bran. *Asian Pacific Journal of Tropical Biomedicine* **8**, 79-84.

29. Sivamaruthi BS, Alagarsamy K, Thangaleela S *et al.* (2023) Composition, microbiota, mechanisms, and anti-obesity properties of Rice bran. *Foods* **12**, 1300.

30. Noormohammadi M, Ghorbani Z, Shahinfar H *et al.* (2023) Is there any hepatic impact associated with rice bran arabinoxylan compound supplementation? A systematic review and

dose–response meta-analysis of randomized controlled trials. *Clinical Nutrition ESPEN* **57**, 665-675.

31. Ghorbani Z, Shoaibinobarian N, Zamani E *et al.* (2025) Supplementing the standard diet with brown rice bran powder might effectively improve metabolic syndrome characteristics and antioxidant status: an open label randomized controlled trial. *Food & Function*.

32. Committee USDGA (2010) *Dietary guidelines for Americans, 2010*: US Department of Health and Human Services, US Department of Agriculture.

33. Lindeman A, Huang M, Dawkins E (2016) Using the Visual Analog Scale (VAS) to measure perceived hunger and satiety at various mealtimes and environments. *Journal of the Academy of Nutrition and Dietetics* **9**, A99.

34. Parker BA, Sturm K, MacIntosh C *et al.* (2004) Relation between food intake and visual analogue scale ratings of appetite and other sensations in healthy older and young subjects. *European journal of clinical nutrition* **58**, 212-218.

35. Tahavorgar A, Vafa M, Shidfar F *et al.* (2014) Whey protein preloads are more beneficial than soy protein preloads in regulating appetite, calorie intake, anthropometry, and body composition of overweight and obese men. *Nutrition research* **34**, 856-861.

36. Beck AT, Steer RA, Carbin MG (1988) Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical psychology review* **8**, 77-100.

37. Beck AT, Ward CH, Mendelson M *et al.* (1961) An inventory for measuring depression. *Archives of general psychiatry* **4**, 561-571.

38. Tecer D, Sunar I, Ozdemirel AE *et al.* (2019) Usefullnes of atherogenic indices and Ca-LDL level to predict subclinical atherosclerosis in patients with psoriatic arthritis? *Advances in Rheumatology* **59**, 49.

39. Oguntola SO, Hassan MO, Duarte R *et al.* (2018) Atherosclerotic vascular disease and its correlates in stable black South African kidney transplant recipients. *Int J Nephrol Renovasc Dis* **11**, 187-193.

40. Yu X, Wang L, Zhang W *et al.* (2019) Fasting triglycerides and glucose index is more suitable for the identification of metabolically unhealthy individuals in the Chinese adult population: A nationwide study. *J Diabetes Investig* **10**, 1050-1058.

41. Dobiásová M, Frohlich J (2001) The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). *Clin Biochem* **34**, 583-588.

42. Cai G, Shi G, Xue S *et al.* (2017) The atherogenic index of plasma is a strong and independent predictor for coronary artery disease in the Chinese Han population. *Medicine (Baltimore)* **96**, e8058.

43. Akpınar O, Bozkurt A, Acartürk E *et al.* (2013) A new index (CHOLINDEX) in detecting coronary artery disease risk. *Anadolu Kardiyol Derg* **13**, 315-319.

44. Olamoyegun MA, Oluyombo R, Asaolu SO (2016) Evaluation of dyslipidemia, lipid ratios, and atherogenic index as cardiovascular risk factors among semi-urban dwellers in Nigeria. *Ann Afr Med* **15**, 194-199.

45. Bello-Chavolla OY, Almeda-Valdes P, Gomez-Velasco D *et al.* (2018) METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity and incident type 2 diabetes. *European journal of endocrinology* **178**, 533-544.

46. Ito Y, Nakashima Y, Matsuoka S (2015) Rice bran extract containing acylated steryl glucoside fraction decreases elevated blood LDL cholesterol level in obese Japanese men. *The Journal of Medical Investigation* **62**, 80-84.

47. Triffoni-Melo AT, Castro M, Jordão AA *et al.* (2023) HIGH-FIBER DIET PROMOTES METABOLIC, HORMONAL, AND SATIETY EFFECTS IN OBESE WOMEN ON A SHORT-TERM CALORIC RESTRICTION. *Arq Gastroenterol* **60**, 163-171.

48. Juvonen KR, Purhonen A-K, Salmenkallio-Marttila M *et al.* (2009) Viscosity of oat bran-enriched beverages influences gastrointestinal hormonal responses in healthy humans. *The Journal of nutrition* **139**, 461-466.

49. Kim IS, Park SY, Park MJ *et al.* (2024) Effect of Barley on Postprandial Blood Glucose Response and Appetite in Healthy Individuals: A Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients* **16**.

50. Wang Z, Wang W, Xu S *et al.* (2023) Diets enriched with finely ground wheat bran alter digesta passage rate and composition of the gut microbiome in sows. *Animal Nutrition* **12**, 32-41.

51. Golloso-Gubat MJ, Magtibay EVJ, Nacis JS *et al.* (2016) Postprandial satiety responses and ghrelin levels with consumption of white rice and brown rice in selected Filipino adults. *Philipp J Sci* **145**, 405-412.

52. Wolever TM, Tosh SM, Spruill SE *et al.* (2020) Increasing oat β-glucan viscosity in a breakfast meal slows gastric emptying and reduces glycemic and insulinemic responses but has no effect on appetite, food intake, or plasma ghrelin and PYY responses in healthy humans: A randomized, placebo-controlled, crossover trial. *The American Journal of Clinical Nutrition* **111**, 319-328.

53. Koliaki C, Kokkinos A, Tentolouris N *et al.* (2010) The effect of ingested macronutrients on postprandial ghrelin response: a critical review of existing literature data. *International journal of peptides* **2010**.

54. Ukkola O (2011) Ghrelin in Type 2 diabetes mellitus and metabolic syndrome. *Molecular and cellular endocrinology* **340**, 26-28.

55. Tsaban G, Yaskolka Meir A, Zelicha H *et al.* (2022) Diet-induced Fasting Ghrelin Elevation Reflects the Recovery of Insulin Sensitivity and Visceral Adiposity Regression. *The Journal of Clinical Endocrinology & Metabolism* **107**, 336-345.

56. Cummings DE, Weigle DS, Frayo RS *et al.* (2002) Plasma Ghrelin Levels after Diet-Induced Weight Loss or Gastric Bypass Surgery. *New England Journal of Medicine* **346**, 1623-1630.

57. Bornhorst GM, Chang LQ, Rutherfurd SM *et al.* (2013) Gastric emptying rate and chyme characteristics for cooked brown and white rice meals in vivo. *Journal of the Science of Food and Agriculture* **93**, 2900-2908.

58. Bornhorst GM, Kostlan K, Singh RP (2013) Particle size distribution of brown and white rice during gastric digestion measured by image analysis. *Journal of food science* **78**, E1383-E1391.

59. Kristensen M, Jensen MG (2011) Dietary fibres in the regulation of appetite and food intake. Importance of viscosity. *Appetite* **56**, 65-70.

60. Klosterbuer AS, Greaves KA, Slavin J (2012) Fiber intake inconsistently alters gut hormone levels in humans following acute or chronic intake. *J Food Res* **1**, 255-273.

61. Mahdavi-Roshan M, Salari A, Kheirkhah J *et al.* (2022) The Effects of Probiotics on Inflammation, Endothelial Dysfunction, and Atherosclerosis Progression: A Mechanistic Overview. *Heart Lung Circ* **31**, e45-e71.

62. Salari A, Mahdavi-Roshan M, Kheirkhah J *et al.* (2021) Probiotics supplementation and cardiometabolic risk factors: A new insight into recent advances, potential mechanisms, and clinical implications. *PharmaNutrition* **16**, 100261.

63. Chang UJ, Hong YH, Jung EY *et al.* (2014) Rice and the glycemic index. In *Wheat and rice in disease prevention and health*, pp. 357-363: Elsevier.

64. Flanagan DE, Evans ML, Monsod TP *et al.* (2003) The influence of insulin on circulating ghrelin. *American Journal of Physiology-Endocrinology and Metabolism* **284**, E313-E316.

65. Delhanty PJ, Neggers SJ, Van der Lely AJ (2012) Mechanisms in endocrinology: Ghrelin: the differences between acyl-and des-acyl ghrelin. *European journal of endocrinology* **167**, 601-608.

66. Thom G, McIntosh A, Messow CM *et al.* (2021) Weight loss-induced increase in fasting ghrelin concentration is a predictor of weight regain: Evidence from the Diabetes Remission Clinical Trial (DiRECT). **23**, 711-719.

67. Mamiya T, Kise M, Morikawa K *et al.* (2007) Effects of pre-germinated brown rice on depression-like behavior in mice. *Pharmacology Biochemistry and Behavior* **86**, 62-67.

68. Um MY, Kim M, Yoon M *et al.* (2023) A novel properties of rice bran: rice bran supplement alleviates chronic restraint stress-induced depression-like behaviors in mice.

69. Mehdi B, Haleem D (2018) Long-term administration of rice bran oil attenuates 5-HT-1A receptor dependent responses in rats. *J Anim Res & Nutr* **3**, 5.

70. Lindqvist D, Dhabhar FS, James SJ *et al.* (2017) Oxidative stress, inflammation and treatment response in major depression. *Psychoneuroendocrinology* **76**, 197-205.

71. Saphyakhajorn W, Sirirat R, Sapwarobol S (2022) Effect of defatted rice bran supplementation on metabolic parameters and inflammatory status in overweight/obese adults with hypercholesterolemia: a randomized, placebo-controlled intervention. *BMC Nutr* **8**, 94.

72. Hongu N, Kitts DD, Zawistowski J *et al.* (2014) Pigmented rice bran and plant sterol combination reduces serum lipids in overweight and obese adults. *J Am Coll Nutr* **33**, 231-238.

73. Liu Q, Zhao J, Liu S *et al.* (2021) Positive intervention of insoluble dietary fiber from defatted rice bran on hyperlipidemia in high fat diet fed rats. *J Food Sci* **86**, 3964-3974.

74. Cheng HH, Huang HY, Chen YY *et al.* (2010) Ameliorative effects of stabilized rice bran on type 2 diabetes patients. *Ann Nutr Metab* **56**, 45-51.

75. Nhung BT, Tuyen LD, Linh VA *et al.* (2016) Rice Bran Extract Reduces the Risk of Atherosclerosis in Post-Menopausal Vietnamese Women. *J Nutr Sci Vitaminol (Tokyo)* **62**, 295-302.

76. Borresen EC, Jenkins-Puccetti N, Schmitz K *et al.* (2017) A Pilot Randomized Controlled Clinical Trial to Assess Tolerance and Efficacy of Navy Bean and Rice Bran Supplementation for Lowering Cholesterol in Children. *Glob Pediatr Health* **4**, 2333794x17694231.

77. Li KJ, Borresen EC, Jenkins-Puccetti N *et al.* (2018) Navy Bean and Rice Bran Intake Alters the Plasma Metabolome of Children at Risk for Cardiovascular Disease. *Frontiers in Nutrition* **4**.

78. Hundemer JK, Nabar SP, Shriver BJ *et al.* (1991) Dietary fiber sources lower blood cholesterol in C57BL/6 mice. *The Journal of nutrition* **121**, 1360-1365.

79. Mahdavi-Roshan M, Salari A, Kheirkhah J *et al.* (2022) The Effects of Probiotics on Inflammation, Endothelial Dysfunction, and Atherosclerosis Progression: A Mechanistic Overview. *Heart, Lung and Circulation* **31**, e45-e71.

80. Golzarand M, Toolabi K, Eskandari Delfan S *et al.* (2022) The effect of brown rice compared to white rice on adiposity indices, lipid profile, and glycemic markers: a systematic review and meta-analysis of randomized controlled trials. *Critical Reviews in Food Science and Nutrition* **62**, 7395-7412.

81. Mohamed MA, Ahmed MA, Abd Elbast SA *et al.* (2019) Rice bran oil ameliorates hepatic insulin resistance by improving insulin signaling in fructose fed-rats. *Journal of Diabetes & Metabolic Disorders* **18**, 89-97.

Table 1. Baseline demographic and clinical data of studied patients with metabolic syndrome in a randomized controlled trial of standard diet + rice bran powder vs. standard diet alone.

		Control group (N=19)	**Intervention group (N=24)**	**P-value**
Age (year)		49 (7)	52 (9)	0.211*
Sex	Female	10 (53%)	11 (46%)	0.763#
	Male	9 (47%)	13 (54%)	
Body mass index (kg/m2)		32.19 (3.12)	32.48 (5.00)	0.826*
Systolic blood pressure (mmHg)		139 (2)	138 (10)	0.880*
Diastolic blood pressure (mmHg)		83 (7)	87 (8)	0.130*
Triglycerides (mmol/L)		2.12 (0.93)	2.37 (1.04)	0.413*
Total cholesterol (mmol/L)		4.55 (1.16)	6.17 (2.34)	0.009*
Low-density lipoprotein-cholesterol (LDL-C) (mmol/L)		2.71 (0.65)	3.01 (0.97)	0.253*
High-density lipoprotein-cholesterol (HDL-C) (mmol/L)		0.96 (0.16)	0.92 (0.13)	0.344*
Fasting blood sugar (FBS) (mmol/L)		7.40 (3.16)	7.92 (2.51)	0.544*

Data are reported as mean (standard deviation, SD) unless otherwise specified.

*Independent sample t-test

Chi square test

The data presented in the current table has been previously published in [31], albeit in a slightly different format.

Table 2. Changes in serum ghrelin, appetite and depression ratings before and after consumption of brown rice bran powder plus standard diet compared to standard diet alone in a randomized controlled trial on patients with metabolic syndrome.

Model	Time point	Control group (N=19)	Intervention group (N=24)	Cohen's d (95%CI)	P-value
Serum Ghrelin level (ng/ml)	**Before**	0.81 (0.26)	0.70 (0.23)	-	0.152*
	After	0.65 (0.20)	0.83 (0.18)	0.95 (0.30, 1.58)	0.008¥
The VAS score of Hunger	**Before**	7.89 (1.70)	8.16 (1.40)	-	0.568*
	After	7.38 (1.48)	6.33 (1.47)	-0.71 (-1.33 - -0.08)	0.026£
The VAS score of Satiety	**Before**	4.95 (1.84)	4.83 (1.66)	-	0.832*
	After	5.23 (1.68)	7.15 (1.67)	1.14 (0.49 -1.79)	<0.001£
The VAS score of Fullness	**Before**	5.36 (1.64)	5.00 (1.14)	-	0.391*
	After	5.08 (1.17)	6.65 (1.16)	1.34 (0.67 – 2.00)	<0.001£
The VAS score of Desire to eat	**Before**	6.47 (2.11)	6.96 (1.43)	-	0.376*
	After	6.24 (1.04)	6.14 (1.03)	-0.10 (-0.70 -0.50)	0.750£
Beck Depression Inventory (BDI) score	**Before**	14.16 (4.71)	13.79 (4.61)	-	0.799*
	After	13.74 (4.07)	9.75 (4.07)	-0.98 (-1.61 - -0.34)	0.003£

Data are reported as mean (standard deviation, SD) unless otherwise specified.
*Independent sample t-test
¥ Analysis of covariance (ANCOVA) adjusted for baseline values and mean changes in body mass index (BMI).
£ ANCOVA adjusted for baseline values.
Cohen's d effect size: measured as the mean difference in change divided by the pooled standard deviation of the change, based on values adjusted for baseline.

Table 3. Changes in atherogenicity and insulin resistance indices before and after consumption of brown rice bran powder plus standard diet compared to standard diet alone in a randomized controlled trial on patients with metabolic syndrome.

Model	Time point	Control group (N=19)	Intervention group (N=24)	Cohen's d (95%CI)	P-value
Atherogenic coefficient (AC)	**Before**	3.87 (1.51)	5.99 (3.07)	-	0.009*
	After	3.48 (0.99)	2.54 (0.98)	-0.94 (-1.57 - -0.30)	0.005£
Castelli risk index-II (CRI-II)	**Before**	2.91 (0.87)	3.40 (1.27)	-	0.157*
	After	2.34 (0.68)	1.69 (0.67)	-0.96 (-1.60 - -0.32)	0.003£
Triglyceride glucose (TyG) index	**Before**	9.29 (0.55)	9.49 (0.56)	-	0.260*
	After	9.35 (0.47)	9.10 (0.46)	-0.54 (-1.15 - 0.08)	0.090£
Atherogenic index of plasma (AIP)	**Before**	0.32 (0.19)	0.38 (0.21)	-	0.345*
	After	0.29 (0.16)	0.20 (0.16)	-0.53 (-1.14 - 0.09)	0.096£
Lipoprotein combine index (LCI)	**Before**	31.07 (25.31)	61.37 (58.94)	-	0.043*
	After	25.94 (19.04)	14.94 (18.93)	-0.58 (-1.19 - 0.04)	0.073£
Cholesterol index (CHOLINDEX)	**Before**	1.75 (0.69)	2.09 (1.04)	-	0.223*
	After	1.34 (0.73)	0.75 (0.72)	-0.81 (-1.43 - -0.18)	0.013£
Metabolic score for insulin resistance (METS−IR)	**Before**	54.52 (7.25)	56.42 (9.36)	-	0.470*
	After	54.49 (2.99)	49.28 (2.98)	-1.74 (-2.45 - -1.03)	<0.001£

Data are reported as mean (standard deviation, SD) unless otherwise specified.

*Independent sample t-test

£ Analysis of covariance (ANCOVA) adjusted for baseline values.

Cohen's d effect size: measured as the mean difference in change divided by the pooled standard deviation of the change, based on values adjusted for baseline.

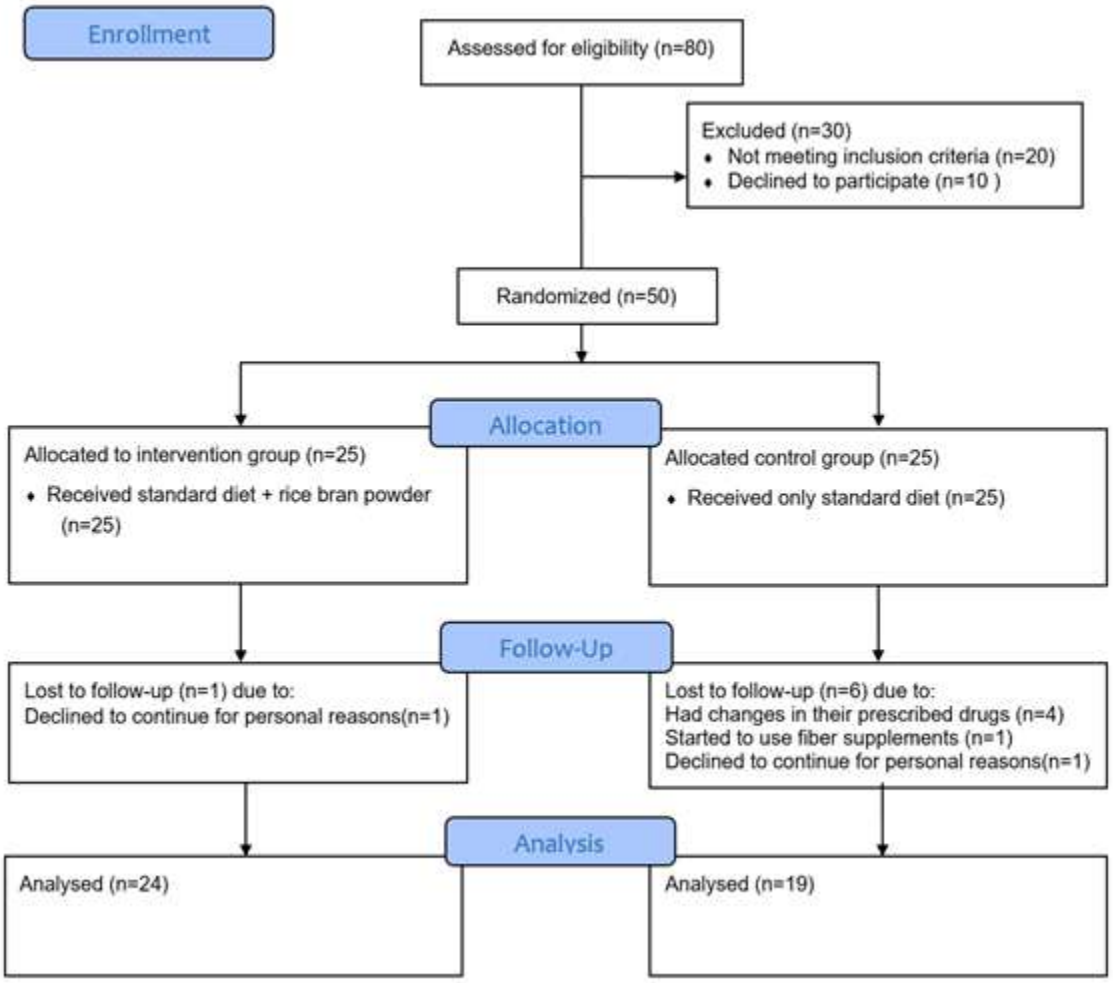

Figure 1. Flow-Diagram of Studied Patients.

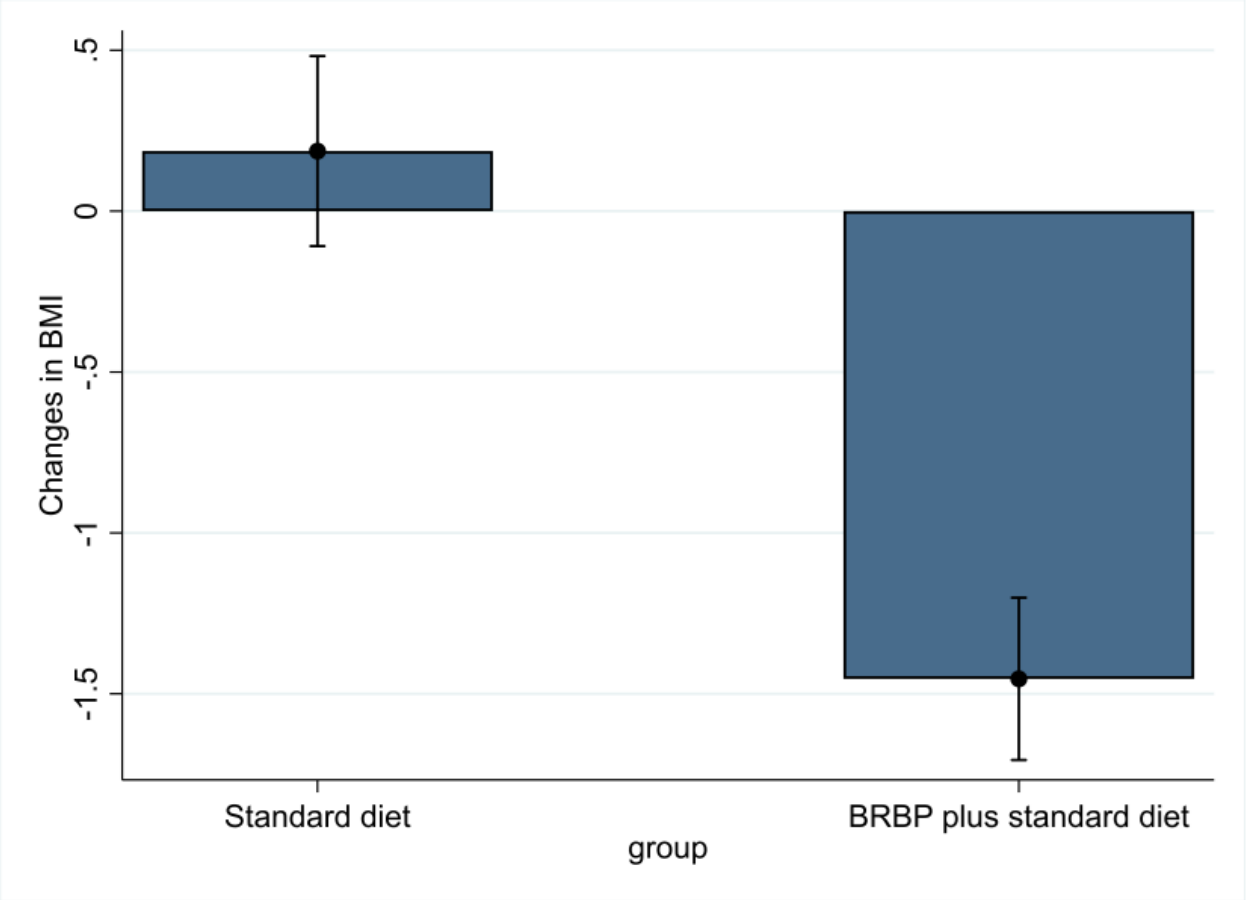

Figure 2: Bar plot illustrating the mean changes in Body Mass Index (BMI) before and after consumption of brown rice bran powder (BRBP) plus standard diet compared to standard diet alone in a randomized controlled trial on patients with metabolic syndrome. Each bar represents the mean BMI change for the respective group. Error bars indicate the standard error of the mean.