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Clinical and psychological responses to synbiotic supplementation in obese or overweight adults: A randomized clinical trial

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ABSTRACT

Background: Obesity is highly prevalent worldwide. Emerging clinical studies suggest that pre- and pro- biotic formulations may be effective interventions for the management of obesity and associated metabolic complications. The current trial was conducted to assess the effect of synbiotic supplementation on anthropometric indices, glycemic and lipid profile, blood pressure, and psychological status of adults with overweight or obesity.
Methods: This randomized double-blind, placebo-controlled trial was conducted on 60 adults with overweight or obesity. Participants were randomly assigned into two groups to receive either synbiotics (n = 30) in form of a 500 mg capsule (containing Lactobacillus acidophilus, *Lactobacillus casei* and *Bifidobacterium bifidum* plus inulin) or placebo (n = 30) for 8 weeks. The level of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FPG), insulin, body weight, body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), stress, anxiety, and depression were measured at the baseline and end of the study.
Results: In total, 59 subjects (39 men and 20 women) completed the present study. A significant between-group decrease in body weight (P = 0.03), TC (P = 0.01), TG (P = 0.02), LDL-C (P = 0.01), stress (P < 0.001), anxiety (P = 0.03), and depression (P = 0.03) was found in the synbiotic group compared to the placebo. However, synbiotics had no significant effect on HDL-C, SBP, DBP, FPG and fasting insulin concentrations, as well the BMI and WC (P < 0.05).
Conclusion: The present study showed that synbiotic supplementation can confer a number of health benefits including improvements in TG, TC, LDL-C, body weight, stress, anxiety, and depression to subjects that are overweight or obesity.
Trial registration: Iranian Registry of Clinical Trials IRCT20180201038585N3.

1. Introduction

Obesity is one of the most widespread chronic diseases around the world, resulting from a complex interaction between eating habits as well as environmental and genetic factors[1–3] Based on World Health Organization statistics, more than 1.9 billion adults are overweight and approximately 650 million people are suffering from obesity.[4] If present trends continue, 2.16 and 1.12 billion adults will be overweight or obese by 2030, respectively.[5] Furthermore, individuals with obesity have a higher risk of numerous metabolic derangements including type 2 diabetes, atherosclerosis, cardiovascular diseases, non-alcoholic fatty liver disease, osteoarthritis, reproductive problems and some forms of cancer.[1,6–8] Obesity also has a negative effect on self-esteem and is bi-directionally associated with depression.[9,10] Lifestyle and pharmacological interventions are two of the most important strategies for obesity management.[11–13] However, stringent lifestyle changes are often only accepted by limited numbers of people and anti-obesity medications may exert some adverse effects while their efficacy is often attenuated

Abbreviations: FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; IPAQ, International Physical Activity Questionnaire; DASS-21, depression anxiety stress scale-21; SCFA, short-chain fatty acids

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after prolonged use.[14] Thus, an important unmet need is the lack of convenient and effective adjuvant therapies for obesity management.

Emerging evidence indicates that adverse changes in the composition of the gut microbiome may play a pivotal role in progression of obesity.[15–17] Probiotic interventions may therefore contribute to the management of obesity and associated complications by influencing the abundance and function of gut microbiota.[15,16,18] Prebiotics can enhance the proliferation of probiotics, resulting in sustainable changes in the human microbiome. Therefore, the combination of pre- and probiotic (synbiotic) interventions may provide a synergistic and effective therapy for metabolic disorders.[19–22] Furthermore, the positive role of synbiotic supplementation in mental diseases such as major depressive disorder have been documented.[23–25] Probiotics might improve symptoms of depression through enhancing tryptophan metabolism and decreasing dopamine metabolite concentrations in the amygdaloid cortex.[26] Based on the current evidence, there is a general lack of research investigating the effects of synbiotics on psychological status in these patients. Therefore, the aim of this study was to assess the effects of synbiotic supplementation on clinical and metabolic response among overweight or obese adults.

2. Materials and methods

2.1. Ethical approval of the study protocol

This study was conducted according to the guidelines established in the Declaration of Helsinki, the CONOSRT guidelines for clinical trial reporting [27] and approved by the Ethics Committee of the Baqiyatallah University of Medical Sciences (IR.BMSU.REC.1397.109). It was also registered at www.irct.ir (Iranian Registry of Clinical Trials ID: IRCT20180201038585N3). Informed consent was obtained from all participants after a full explanation of the purpose and nature of all procedures involved.

2.2. Participants

Sixty overweight or obese subjects were enrolled in present double-blind, randomized, controlled clinical trial from the Shahid Sadoughi Hospital in Isfahan, Iran from December 2018 to February 2019. To determine sample size, mean (standard deviation; SD) of fasting blood glucose (FBG) was used from a previous clinical trial on the effects of synbiotics on metabolic response of obese adults.[28] A minimum sample size of 22 participants was calculated with a confidence level of 95% and a power of 90% per treatment group. Considering an attrition rate of 20%, the sample size was increased to 30 in each group.

Inclusion criteria were as follows: men or women between the ages of 20–50 with a body mass index (BMI) greater than 25 and less than 35 kg/m^2. Subjects were excluded if they had a history of cardiovascular, renal, hepatic, or pancreatic diseases, diabetes, hypertension, inflammatory or infectious disease, neurological or psychiatric disorders, thyroid dysfunctions, and malignancy, if they were following a weight-loss diet or prescribed any weight loss medications during the last year, smoked, were pregnant or lactating, were taking alcohol, herbal drugs, antidepressant drugs, prebiotic or probiotic products, or any other supplements/drugs which could interfere with the study objectives.

Participants were matched for age, sex, BMI, and randomly divided into two groups of synbiotics and control using random allocation software. Randomization was done by one researchers who had no clinical involvement in the trial. Subjects in the treatment group received one capsule of synbiotics and control group subjects received one placebo capsule (starch) that they were required to take daily for 8 weeks. Synbiotic supplements in form of a 500 mg capsule contained Lactobacillus acidophilus, *Lactobacillus casei* and *Bifidobacterium bifidum* (2×10^9 CFU/g each) plus 0.8 g inulin. The appearance of the placebo was indistinguishable in color, shape, size, packaging, and taste from the synbiotic capsule. Synbiotic supplements and placebos were produced by Tak Gen Zist Pharmaceutical Company. All participants were advised to maintain their usual diet and physical activity during the intervention period. The subjects were reminded by phone to ensure compliance and empty bottles of synbiotics were returned after completion. A checklist was also applied to record any possible adverse reactions.

2.3. Dietary intake assessment

To obtain detailed information regarding participant dietary intake and physical activity, participants were asked at the onset and end of the study to complete 3-day food records (one weekend day and two week days) and the International Physical Activity Questionnaire (IPAQ), a valid and reliable self-administered questionnaire that contains 5 activity domains.[29] Physical activity was calculated as a metabolic equivalent task minute per week spent on all activities. The dietary data were analyzed using the Nutritionist IV software program (First Databank, Inc., Hearst Corporation) using the database from tables of content and nutritional value of Iranian food products.

2.4. Measurement of anthropometric parameters and blood pressure

Anthropometric measurements of height and body weight, as well as waist circumferences (WC), were made at baseline and the end point of the study. Height was measured by a wall-mounted stadiometer to the nearest 0·5 cm; weight was measured in light clothing and barefoot to the nearest 0·1 kg. WC was measured to the nearest 0·1 cm using a flexible tape at the mid-point between the lowest rib and the iliac crest. BMI was calculated by using the following formula: BMI = weight (kg)/height $(m)^2$. All the measurements were taken by the same person to decrease the error rate. Each participant's blood pressure was measured by a trained nurse on two occasions, before and after sitting for a 15 min period, using a mercury sphygmomanometer; the mean blood pressure reading was used for the present analysis.

2.5. Biochemical assessment

At baseline and after 8 weeks of supplementation, 10 ml venous blood samples were collected after 10–12 h of fasting between 8 a.m. and 9 a.m.. Blood samples were centrifuged at 3000 g for 10 min and serum was isolated and frozen at −80 °C until analysis. Levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), FPG and fasting insulin concentrations were measured by enzymatic means (Pars Azmoun, Tehran, Iran).

Assessment of psychological status

Depression, anxiety and stress symptomatology was assessed in all study participants using the a translated version of the Depression Anxiety Stress Scale-21 (DASS-21),[30] which has been shown to be validated and reliable in the Persian adult general population with psychometric properties similar to those reported in the international literature.[31] Briefly, the DASS-21 consists of 21 self-reported items with seven items in each of the three subscales for depression, anxiety, and stress. The respondent scores each item based on frequency or severity of emotional experiences over the last week on four-point scale ranged from 0 to 3. The score of 0 considered that the item "no symptoms at all" to 3 that indicates the item was "very severe". Scores from the seven items in each subscale are summed up to yield a single subscale score. Each of these subscale scores is further multiplied by two (subscale score range: 0–42) in order to compare it with the normative data of the long form of the DASS instrument which has 42 items (DASS-42). Notably, the DASS-21 has the same factor structure and yields similar results to the DASS-42, while requiring half the time to be administered (5–10 min s). Subscale scores equal or higher than 10, 8 and 15 indicate the presence of at least mild depression, anxiety and stress

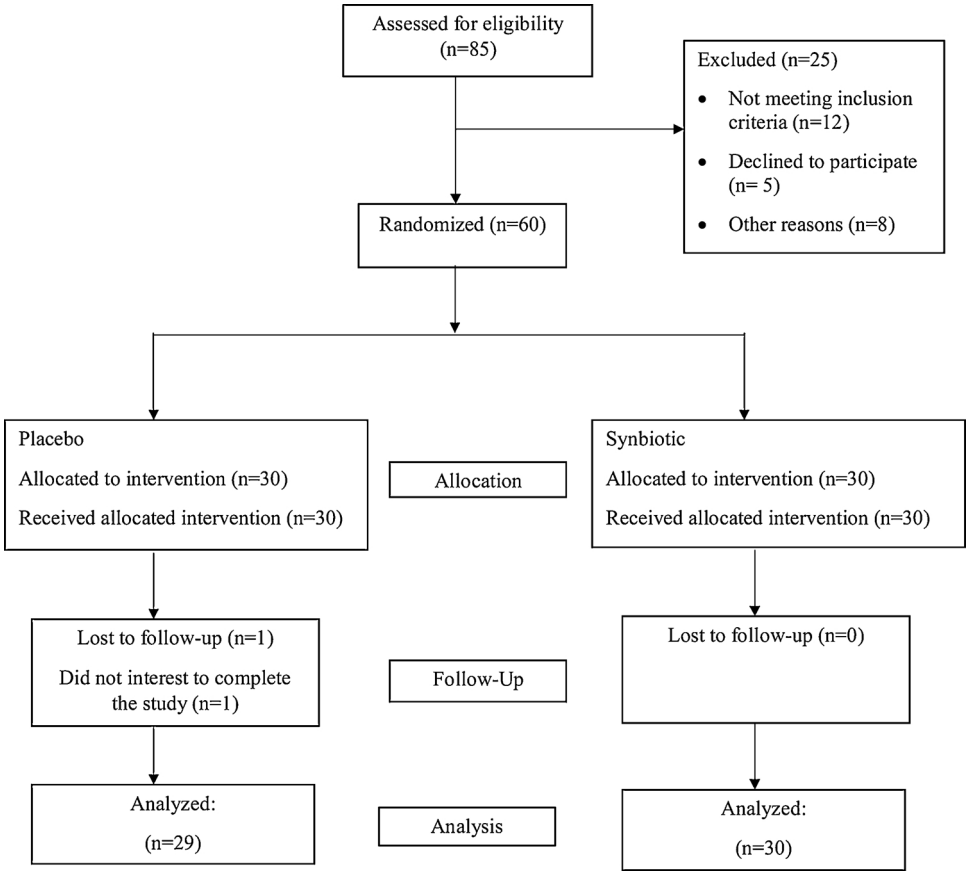

Fig. 1. Flow diagram of the enrolled participants.

Table 1
General characteristics of study participants (Mean values and standard deviations).

Variables	Synbiotic (N = 30)	Placebo (N = 29)	P-value
Age (year)	34.49 ± 6.02	36.64 ± 7.26	0.23
Height (cm)	172.3 ± 6.6	170.1 ± 7.3	0.79
Sex (F/M)	11 F/ 19M	9F/ 20 M	0.58
Body weight (kg)	88.43 ± 10.50	85.91 ± 9.19	0.33
BMI (kg/m^2)	31.40 ± 3.73	30.33 ± 3.24	0.24
Waist circumference	101.79 ± 6.85	100.91 ± 7.75	0.64
SBP (mmHg)	119.28 ± 6.61	121.11 ± 8.81	0.37
DBP (mmHg)	79.15 ± 6.7	77.38 ± 7.11	0.32
FPG (mg/dl)	99.71 ± 9.47	98.26 ± 9.37	0.55
Fasting Insulin (μIU/ml)	13.39 ± 5.11	14.28 ± 4.63	0.48

P-value was obtained from Independent samples *t*-test.
Abbreviations: BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose.

symptomatology, respectively. Higher scores in each subscale indicate even greater severity of the corresponding depression, anxiety and stress symptoms.

2.6. Statistical methods

The Statistical Package for Social Science version 16 (SPSS Inc., Chicago, IL, USA) was applied to carry out all analyses. Normality of the variables was tested with the Kolmogorov-Smirnov test. To compare changes between the start and end of the intervention in each group, paired *t*-test was used for the data with normal distribution and Wilcoxon signed-rank test was used for skewed data. One-way ANCOVA test was used for variations among groups and Bonferroni post-hoc test was used to compare the two groups with normal distribution. Kruskal–Wallis test was used in the case of abnormal distribution. Results were expressed as mean ± SD. $P < 0.05$ was considered as significant.

3. Results

The flow chart of participants through the trial is presented in Fig. 1. Eighty-five overweight/obese adults were primarily assessed against the inclusion and exclusion criteria. Sixty participants met the criteria and were randomly assigned into the synbiotics or placebo group. Only one participant was excluded from the placebo group during follow-up phase due to an unwillingness to continue the study. Therefore, 59 subjects completed the trial and included to final analysis. Compliance rate of study was high in both groups based on number of untaken capsule (< 5%) which were returned by participants throughout the study.

3.1. Demographics

Table 1 presents the baseline characteristics of participants in both synbiotics and placebo groups. There is no significant difference between two groups in term of age, sex, height, anthropometric indices and metabolic parameters at baseline.

3.2. Physical activity and dietary intake

Based on the 3-day dietary records throughout the study, no statistically significant difference was seen between the two groups in terms of dietary intakes of energy, carbohydrate, protein, fat and fiber. In addition, no remarkable difference was detected between synbiotics and placebo group in physical activity at beginning and end of treatment. Also, physical activity level of the participants remained

Table 2
Dietary intakes and physical activity of study participants throughout the study (Mean values and standard deviations).

Variables	Synbiotic (N = 30)			Placebo (N = 29)			
	Baseline	At 8 weeks	P-value[1]	Baseline	At 8 weeks	P-value[1]	P-value[2]
Energy (kcal/day)	2298.87 ± 238.60	2272.12 ± 189.08	0.40	2177.52 ± 270.15	2157.41 ± 304.47	0.57	0.88
Carbohydrate (g/day)	337.46 ± 35.54	333.07 ± 43.45	0.55	314.68 ± 70.22	318.19 ± 48.58	0.76	0.78
FAT (g/day)	63.85 ± 6.62	63.13 ± 9.72	0.63	62.53 ± 12.37	60.16 ± 8.27	0.25	0.48
Protein (g/day)	95.44 ± 18.49	97.62 ± 18.72	0.67	89.30 ± 13.30	85.71 ± 14.12	0.40	0.63
Fiber (g/day)	15.07 ± 7.31	14.07 ± 6.31	0.43	13.83 ± 6.91	14.84 ± 7.31	0.49	0.73
Physical activity (MET-h/day)	28.52 ± 2.87	28.22 ± 2.98	0.53	27.81 ± 2.43	27.73 ± 2.57	0.72	0.48

P- Value < 0.05 was significant.
P-value[1]was obtained from paired *t*-test.
P-value[2] was obtained from ANOVA.

unchanged throughout the study (Table 2). No serious adverse effect was reported among participants following the supplementation of synbiotics.

3.3. Findings recorded in the two groups of participants before and after treatment

At the end of the treatment, we found a greater reduction in TG (-5.92 ± 7.43 vs 0.27 ± 12.76; P = 0.02), TC (-10.12 ± 14.28 vs -0.14 ± 17.16; P = 0.01), LDL-C (-9.38 ± 17.52 vs -0.09 ± 12.24; P = 0.02) and body weight (-4.01 ± 4.05 vs -1.89 ± 3.23; P = 0.03) in individuals with synbiotic administration compared to placebo.

Synbiotics resulted in a significant improvement in stress (-3.49 ± 2.30 vs -1.41 ± 3.44; P < 0.001), anxiety (-2.61 ± 1.49 vs -1.46 ± 2.49; P = 0.03), depression (-2.86 ± 2.47 vs -1.54 ± 2.13; P = 0.03) when compared to placebo. Furthermore, a trend to toward a significant decrease was found in BMI (-1.31 ± 1.42 vs -0.66 ± 1.14; P = 0.06) and WC (-0.89 ± 1.47 vs -0.35 ± 0.83; P = 0.08), in synbiotics group comparing placebo. However, synbiotic supplementation had no significant effect on HDL-C, SBP, DBP, FPG and fasting insulin concentrations (P < 0.05) (Table 3).

4. Discussion

The current study found that synbiotic supplementation for 8 weeks led to significant improvements in TG, TC, LDL-C, body weight, BMI, WC, stress, anxiety, and depression. However, no significant between-group difference was found for HDL-C, SBP, DBP, FPG and fasting insulin concentrations.

In line with the results of this study, a recent 12- week clinical trial among healthy overweight or obese volunteers demonstrated that the administration of one serving/day of whole-grain pasta containing barley β-glucans and *Bacillus coagulans* resulted in significant decreases in LDL/HDL cholesterol ratio, while no alterations in other outcomes were reported.[32] Furthermore, a 2017 meta-analysis (N = 15 trials), reported beneficial effects of probiotic Lactobacillus on TC and LDL-C without any significant effects on TG and HDL-C levels.[33] Some divergence between the results described here compared to previous studies is potentially due to differences in the probiotic strain, study duration, ethnic origin, and dietary context, prior probiotic intake and intra-individual strain differences.[15,34]

While the mechanisms of action of synbiotic interventions on lipid profiles has not been fully elucidated, the reported effect in this study may be at least partially attributed to the effects of the synbiotic on gut microbiota modification, further causing alterations in conversion of cholesterol into coprostanol,[35] assimilation of cholesterol,[36] and enzymatic deconjugation of bile acids by bile-salt hydrolase.[37] Similarly, prebiotic interventions may affect lipid profiles through decreasing cholesterol absorption accompanied by enhanced cholesterol excretion via feces. Fermentation of prebiotics also produce short-chain fatty acids (SCFA) with numerous positive functions including the inhibition of liver cholesterol/ fatty acids synthesis resulting in reduced rates of cholesterol/ triacylglycerol secretion.[37]

This trial also found a significant reduction in body weight.

Table 3
Anthropometric parameters, blood pressure, glycaemia, lipid profile and psychological status of study participants throughout the study.

Variables	Synbiotic (N = 30)				Placebo (N = 29)				
	Baseline	At 8 weeks	Changes	P-value[1]	Baseline	At 8 weeks	Changes	P-value[1]	P-value[2]
Body weight (kg)	88.43 ± 10.50	84.42 ± 9.68	−4.01 ± 4.05	< 0.001	85.91 ± 9.19	84.02 ± 8.44	−1.89 ± 3.23	< 0.001	0.03
BMI (kg/m^2)	31.40 ± 3.73	30.09 ± 3.45	−1.31 ± 1.42	< 0.001	30.33 ± 3.24	29.66 ± 2.98	−0.66 ± 1.14	< 0.001	0.06
Waist circumstance (cm)	101.79 ± 6.85	100.90 ± 6.81	−0.89 ± 1.47	< 0.001	100.91 ± 7.75	100.55 ± 7.81	−0.35 ± 0.83	0.03	0.08
FBG (mg/dl)	99.71 ± 9.47	96.44 ± 8.84	−3.26 ± 8.63	0.04	98.26 ± 9.37	97.67 ± 7.64	−0.58 ± 6.07	0.60	0.17
Fasting Insulin (μIU/ml)	13.39 ± 5.11	12.66 ± 4.57	−0.73 ± 2.09	0.06	14.28 ± 4.63	13.80 ± 4.1	−0.48 ± 1.80	0.16	0.62
TG (md/dl)	173.97 ± 20.97	168.05 ± 18.33	−5.92 ± 7.43	< 0.001	166.00 ± 20.97	166.27 ± 19.50	0.27 ± 12.76	0.91	0.02
TC (mg/dl)	184.24 ± 20.54	174.12 ± 15.39	−10.12 ± 14.28	< 0.001	177.17 ± 24.55	177.02 ± 25.23	−0.14 ± 17.16	0.96	0.01
LDL-c (mg/dl)	134.45 ± 28.78	125.06 ± 22.22	−9.38 ± 17.52	< 0.001	129.57 ± 31.07	129.48 ± 28.31	−0.09 ± 12.24	0.96	0.02
HDL-c (mg/dl)	39.81 ± 6.06	39.28 ± 5.82	−0.52 ± 1.65	0.09	38.05 ± 5.52	38.33 ± 4.99	0.27 ± 2.20	0.50	0.11
SBP (mmHg)	119.28 ± 6.61	118.99 ± 6.38	−0.28 ± 4.3	0.72	121.11 ± 8.81	121.90 ± 7.93	0.79 ± 3.52	0.23	0.30
DBP (mmHg)	79.15 ± 6.7	78.88 ± 5.7	−0.27 ± 1.80	0.41	77.38 ± 7.11	77.45 ± 5.92	0.06 ± 1.73	0.83	0.45
Stress sore	20.06 ± 1.90	16.57 ± 1.31	−3.49 ± 2.30	< 0.001	18.95 ± 2.14	17.55 ± 2.30	−1.41 ± 3.44	0.03	< 0.001
Anxiety score	8.85 ± 1.58	6.23 ± 1.03	−2.61 ± 1.49	< 0.001	8.78 ± 2.25	7.31 ± 1.28	−1.46 ± 2.49	< 0.001	0.03
Depression score	12.20 ± 2.73	9.34 ± 1.54	−2.86 ± 2.47	< 0.001	12.45 ± 2.15	10.91 ± 1.60	−1.54 ± 2.13	< 0.001	0.03

P- Value < 0.05 was significant.
P-value1was obtained from paired *t*-test.
P-value2 was obtained from ANOVA.
Abbreviations: TG: triacylglycerol; TC: total-cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; FBS: fasting blood glucose; BMI: body mass index; WC: waist circumstance; SBP: systolic blood pressure; DBP: diastolic blood pressure.

However, synbiotics did not have a significant effect on BMI and WC compared with the placebo group. Observing no changes in BMI might be due relatively small reduction in weight. Weight adjusted for height, BMI; in kg/m^2 is highly correlated with height.[38,39] Our findings were in line with our recent meta-analysis (N = 23 trials), which examined the effects of synbiotics on anthropometric indices among participants with overweight or obesity.[15] This meta-analysis indicated that supplementation with synbiotics can significantly decrease body weight (−0.80 kg) and waist circumference (−2.07 cm) without any effect on BMI and body fat.

The literature suggests numerous mechanisms by which synbiotic interventions could affect body weight. Novel research shows that certain strains of probiotics by can influence the host's metabolic, neuroendocrine, immune functions,[40,41] body weight regulation,[41] energy storage,[42,43] energy expenditure [43] and also integrate peripheral and central food intake regulatory signals. Similarly, prebiotic intake may affect body weight via production of short chain fatty acids, which inhibit fat accumulation in adipose tissue, increase energy expenditure, and modulate hormones associated with the feeling of satiety.[44]

The findings of the present study also demonstrated a significant improvement in stress, anxiety, and depression. Previous research has reported that 6 weeks intervention with synbiotics can significantly decrease depression symptom compared to the placebo in some[45] but not all[46] previous trials. In this field, a meta-analysis in 2017 suggested that probiotics can reduce psychological symptoms including anxiety, depression, and perceived stress in healthy adult volunteers.[47] Gut microbiota can directly produce, and influence the production of, neurotransmitters such as serotonin.[48] Gut microbiota also possess immunomodulatory functions and is able to activate the hypothalamic-pituitary axis via the production of pro-inflammatory cytokines IL-1 and IL-6.[48] Emerging evidence suggests that probiotic supplementation may also influence both the central nervous system and the enteric nervous system.[49] In addition, the beneficial effect of probiotic supplementation has been even suggested in patients with other psychological and neurological conditions such as clinical depression, schizophrenia, and Alzheimer disease.[23,50,51]

We did not observe any serious side-effects that resulted from synbiotic intake throughout the study. Synbiotic is recognized as safe supplement which is widely used by general population in order to increase health outcomes.[52] Only minor gastrointestinal discomfort including bloating or diarrhea was reported by previously studies.[53,54] While probiotic and symbiotic interventions appear to be well-tolerated, further studies are required to confirm the long-term use of probiotic interventions as well as to evaluate the optimal dose and strain of probiotic formulations.[55,56] There are a variety of probiotic strains with various influences on metabolic parameters and our information around effect of these beneficial bacteria are mostly limited to lactobacilli and bifidobacteria.[57–59] In this regard, there is a need to determine the effects of individual probiotic/synbiotic strains before clinical recommendations are appropriate.

There were some limitations in the present research. The fecal bacterial profiles could not be measured to evaluate the synbiotic consumption which may have provided a more precise method of measuring adherence. Dietary intake was assessed by using 3-day food records which has some biases related to expectation and recall of the participants. Notwithstanding, this study was conducted in a generalizable and clinically relevant population of free-living overweight and obese subjects in both sexes. Moreover, assessment of metabolic factors along with psychological disorders, detailed data collection through face-to-face meetings, small number of participants' drop out, and no major side effects of the treatment are other strengths of current research.

Future studies are required to elucidate the role of individual variation in human genetics and microbiome composition in treatment response. Furthermore, optimal dosing regimens are required for both pre- and pro-biotic interventions before clinical recommendations are warranted.

5. Conclusion

In summary, the results of the present study indicate that consumption of a synbiotic formulation for 8 weeks may improve TG, TC, LDL-C, body weight, stress, anxiety, and depression in subjects with overweight and obesity.

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Declaration of Competing Interest

No other authors declare a conflict of interest.

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