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Modulation of Gut Microbiota for Obesity Management: A Systematic Review

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Abstract

Obesity is a complex chronic disease characterized by excessive fat deposits that affects our health negatively. Current research suggests that gut microbiota may play a role in the development of obesity and its associated health related conditions. Gut microbiota can impact energy extraction from food, lipid metabolism, immune response, and endocrine functions. The composition of gut microbiota has been found to differ between obese and lean individuals. Moreover, it has been found that different obesity treatments affect the diversity and composition of the intestinal microbiome, raising concerns about how these changes might influence weight loss outcomes. Research suggests that probiotics, prebiotics, and synbiotics can influence the release of hormones, neurotransmitters, and inflammatory factors, therefore reducing the triggers for food consumption that contribute to weight gain; however, more research is needed. Several studies on both animals and humans suggest that modifying the bacterial strains in the digestive tract can reshape the metabolic profile of obese individuals. Fecal microbiota transformation has also lately appeared as a treatment possibility in obesity and other metabolic diseases which will also be discussed in this paper. The aim of the following Systematic review is to determine if modulating gut microbiota through probiotics, synbiotics, prebiotic and fecal transplantation can promote weight loss in individuals with obesity and overweight.

RIASSUNTO

L’obesità è una malattia cronica complessa caratterizzata da eccessivi depositi di grasso che influiscono negativamente sulla nostra salute. La ricerca attuale suggerisce che il microbiota intestinale può svolgere un ruolo nello sviluppo dell’obesità e delle condizioni di salute ad essa associate. Il microbiota intestinale può influenzare l’estrazione di energia dal cibo, il metabolismo dei lipidi, la risposta immunitaria e le funzioni endocrine. È stato scoperto che la composizione del microbiota intestinale differisce tra individui obesi e magri. Inoltre, è stato scoperto che diversi trattamenti per l’obesità influenzano la diversità e la composizione del microbioma intestinale, sollevando preoccupazioni su come questi cambiamenti potrebbero influenzare i risultati della perdita di peso. La ricerca suggerisce che probiotici, prebiotici e simbiotici possono influenzare il rilascio di ormoni, neurotrasmettitori e fattori infiammatori, riducendo quindi i fattori scatenanti del consumo di cibo che contribuiscono all’aumento di peso; tuttavia, sono necessarie ulteriori ricerche. Diversi studi sia sugli animali che sull’uomo suggeriscono che la modifica dei ceppi batterici nel tratto digestivo può rimodellare il profilo metabolico degli individui obesi. La trasformazione del microbiota fecale è apparsa recentemente anche come possibilità di trattamento dell’obesità e di altre malattie metaboliche che verranno discusse anche in questo articolo. Lo scopo della seguente meta-analisi è determinare se la modulazione del microbiota intestinale attraverso probiotici, prebiotici, simbiotici e trapianto fecale può promuovere la perdita di peso negli individui con obesità e sovrappeso.

1.0 Introduction

Obesity is characterized by an abnormal or excessive buildup of fat, which is linked to the development of various metabolic diseases such as type 2 diabetes mellitus, cardiovascular disease, nonalcoholic fatty liver disease, and cancer.[1] In 2022, over 1 billion individuals globally were living with obesity. Since 1990, the prevalence of obesity among adults has more than doubled, and it has increased fourfold among children and teenagers aged 5 to 19.[2] Worldwide, 1.5 billion adults are currently either overweight or obese, with this figure projected to rise to 3 billion by 2030.[3] While BMI is often regarded as a rough indicator because it may not reflect the same level of obesity in different people, it is consistent across genders and all adult age groups. Therefore, it serves as the most effective measure of overweight and obesity at the population level and it is associated with critical health outcome such as heart disease, diabetes, cancer, and overall mortality. [3,4] It is calculated using a person's height and weight (BMI = kg/m^2). For adult men and women, a BMI ranging from 18.5 to 24.9 is considered within the healthy range. A BMI between 25.0 and 29.9 is classified as overweight, and a BMI of 30 or higher is categorized as obese. [3] Research comparing BMI with other methods of assessing body fat has shown that at higher BMI levels, BMI yields results similar to those of other techniques, such as dual-energy x-ray absorptiometry. [4] Numerous factors might contribute to the development of obesity such as poor diet, physical inactivity, insufficient sleep, consumption of high fat foods, side effects of some medications, genetic predisposition, and various environmental and social influences [5,6] . However, one of the most intriguing factors explored in recent decades is the impact of gut microbiota. It has been proposed that certain aspects of the gut microbiome, including its composition, diversity, relative abundance, and functional pathways, could make adults more susceptible to obesity. [4] Given the gut microbiota's role in energy balance and the secretion of

appetite-suppressing hormones, altering its composition is a potential strategy for preventing obesity. Emerging evidence underscores those detrimental alterations in this intricate ecosystem, known as the dysbiosis, play a role in the onset and progression of obesity. [7] Consequently, pro-, pre- and synbiotics have garnered significant interest. The Food and Agriculture Organization of the United States (FAO) defines probiotics as cultures of live microorganisms that, when consumed in sufficient quantities and for an appropriate duration, can provide health benefits to the host. The term "synbiotic" refers to dietary supplements that synergistically combine probiotics and prebiotics. Prebiotics consist of fermentable dietary fibers that promote the growth and survival of probiotics, thereby benefiting the host. Probiotics, prebiotics and synbiotics impact the abundance and functions of gut microbiota, potentially aiding in the prevention of obesity. [7] A considerable body of evidence suggests that supplementation with pro-, pre- and synbiotics may positively influence anthropometric and metabolic parameters by modulating the structure and/or functionality of the gut microbiota; however, more research is needed. [7] Moreover, previous research has shown that fecal microbiota transplantation, which involves introducing a donor fecal matter into recipient's intestinal tract, may have beneficial effects for obesity, inflammatory bowel disease metabolic syndrome and functional gastrointestinal disorder.[8] The purpose of this thesis is to systematically review the current available evidence is to see whether the modulation of gut microbiota by probiotic, prebiotic, symbiotic and fecal microbiota transplantation could have a favorable role in the management of obesity among people with obesity and overweight.

1.1 The microbiome and its role

The term ‘microbiota corresponds to the bacteria, archaea, microeukaryotes and viruses that inhabit human internal environment. These microorganisms may operate in a commensal, synergistic or harmful manner. The term ‘microbiota’ applies to the combined genomes of the microbial organisms. [8] The gut contains a trillion microbes, forming a complex microbial community made up of roughly 1000 to 1100 different bacterial species, collectively totaling around 10^{14} to 10^{15} microbes. This microbial population is ten times greater than the number of cells in the host's eukaryotic body.[9] The adult human gut is predominantly populated by bacteria from three primary divisions: Firmicutes (Gram-positive), Bacteroidetes (Gram-negative), and Actinobacteria (Gram-positive). These three groups collectively account for over 90% of the total bacterial population in the gut. [9] The establishment of gut microbiota starts right at birth, as the fetus encounters bacteria for the first time while passing through the birth canal. This exposure explains why the microbiota of infants often resembles the bacterial communities found in their mother's vaginal microbiota.[10] Additionally, there is a well-documented variation in the gut microbiota composition between infants born via caesarean section and those born through vaginal delivery. The gut microbiota undergoes significant changes over the course of a lifetime; however, by the time a child reaches one year of age, the microbiota tends to stabilize and starts to match that of a young adult. This suggests that the initial colonization of the gastrointestinal tract could be a key factor in determining the microbiota's composition in adulthood.[10] Nevertheless, the formation of gut microbiota is a complicated process shaped by various factors. The density and type of the bacterial population in the gastrointestinal (GI) tract are influenced by environmental factors such as pH, oxygen levels, and nutrient availability.[6] Each person has a distinct gut microbiome (GM) composition, shaped by many internal and external factors such as

gestational age, mode of delivery, breastfeeding, antibiotic exposure, diet, and lifestyle The formation of GM varies across the gastrointestinal tract, with sparse distribution in the stomach and small intestine, but a dense and diverse population in the colon [6] . This concentration in the colon is due to the lack of digestive secretions, slower peristalsis, and an abundant nutrient supply. These microbes are crucial in maintaining the host's body homeostasis by aiding in digestion, energy and short chain fatty acid production (SCFA) production, preventing pathogen establishment, synthesizing vitamins (Vitamin B and 12) that human cannot make and improves intestinal barrier function influencing immunological ad inflammatory responses. [6,11,12] The gut microbiome impacts an individual's metabolic functions, including the extraction of calories from indigestible dietary substances and their storage in adipose tissue, which can increase the risk of obesity.[6] It could also have an impact on the brain and central nervous system, which could potentially illustrate the link between gut microbiota and overall health. The gut is known as the 'second brain' that is made up of trillions of microorganisms that have an immediate effect on the brain and brain signals, altering hunger and appetite stimulants.[13]

1.2 Gut microbiota, obesity and dysbiosis

The microbiota has a symbiotic connection with the host and plays an essential role in maintaining human health and managing diseases. Therefore, preserving the homeostatic balance of the intestinal microbiome is highly advantageous for the host. [14] Certain diseases such as autoimmune disorders, allergies, inflammatory bowel disease, and obesity are linked to shifts in microbial composition, leading to significant imbalances between beneficial and possibly harmful bacteria.[14] This disruption in microbial balance is known as "dysbiosis," a condition characterized by an alteration in microbiota homeostasis. It results from a breakdown in the gut's

ecological balance, alterations in microbial gene diversity, shifts in functional composition and metabolic activities, or variation in the spatial microbial distribution. [14] Research indicates the crucial role of gut microbiota (GM) dysbiosis—characterized by alterations in the proportions of different taxa, decreased bacterial diversity and activity, and the presence of bacteria-derived metabolites—in energy imbalance, appetite regulation, metabolic endotoxemia, and bile acid metabolism. These changes might be a contributing factor to obesity and its associated conditions, including type 2 diabetes (T2D), non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), brain disease, obesity and cancer. [4,15] This imbalance in the gut microbiome increases the release of lipopolysaccharide, an endotoxin from the outer membrane of Gram-negative bacteria, which disrupts immunity and compromises the intestinal mucosal barrier. This leads to a "leaky gut" and triggers inflammatory pathways. Bacterial dysbiosis caused by firmicutes species has been associated to changes in gastrointestinal peptides (gastrin, cholecystokinin, somatostatin and ghrelin). These modifications could ultimately end up in decreased satiety, increased appetite and food intake. [13] Growing evidence indicates that energy balance, which involves both energy intake and expenditure, is closely linked and influenced by the gut microbiota. Three primary mechanisms through which the balance of gut microbiota can affect body weight: (1) the production of short-chain fatty acids (SCFAs), (2) the modulation of bile acid metabolism, and (3) the triggering or prevention of metabolic endotoxemia.[16] The GM can regulate energy intake and appetite through the production of short-chain fatty acids (SCFAs) from nondigestible polysaccharides. [1] These SCFAs, including acetate, butyrate, and propionate, are generated through bacterial fermentation and serve both as energy sources and as regulators of satiety and food intake by interacting with G-protein coupled receptors 41 (GPR41) and 43 (GPR43) in intestinal epithelial cells. Additionally, SCFAs promote the release of peptide

YY (PYY) and glucagon-like peptide-1 (GLP-1) [1]. GLP-1 and PYY function as appetite suppressants and are key mediators of the gut-brain axis, facilitating crucial communication related to energy balance, digestion, and appetite. They help reduce intestinal motility and gastric emptying while also playing a role in managing glucose homeostasis, reducing inflammation, improving lipid metabolism, enhancing intestinal barrier and energy use thus having positive effects on body weight. [13,17] Obesity has been associated with low-grade inflammation, which is partly due to the malfunction of intestinal epithelial membrane receptor proteins that serve sensory functions in the gut. This malfunction leads to increased gut permeability and a decrease in the expression of tight junction proteins, allowing bacterial fragments such as lipopolysaccharides (LPS) to pass through the intestinal barrier and enter the bloodstream, causing metabolic endotoxemia. [17] Once in the bloodstream, LPS binds to the pattern recognition receptor CD14, and this complex is identified by toll-like receptor-4 (TLR4), a key element of the innate immune system responsible for maintaining intestinal balance. [17] Individuals consuming a high-fat diet exhibit elevated plasma LPS levels, which activate cells via TLR4 and contribute to the low-grade inflammation characteristic of obesity. Whether due to high-fat diets or experimentally induced methods like infusion, increased plasma LPS concentrations lead to metabolic disturbances and systemic inflammation. These effects are accompanied by a notable decrease in the gut populations of Lactobacillus spp., Bifidobacterium spp., and Bacteroides–Prevotella spp. [17]

The evidence connecting gut microbiota to obesity development was provided by Bäckhed et al., (2004) they transplanted microbiota from normal mice into germ-free (GF) mice. In spite of eating less, the GF mice subsequently gained more fat pad mass and body weight compared to germ free mice that did not receive the microbiota transplantation. This weight gain was

associated with insulin resistance, as well as elevated glucose and leptin levels in the blood. The presence of bacteria increased serum glucose and SCFA levels, leading to liver triglyceride synthesis, increased adiposity, and decreased glucose tolerance. The authors found that microbes in the gut boosted monosaccharide absorption and polysaccharide degradation. The researchers suggested that the transplanted microbiota enabled the GF mice to extract additional energy from their diet. Additionally, they proposed that microbiota boosts the expression of crucial transcription factors to enhance lipogenesis in the liver and stimulates lipoprotein lipase (LPL) activity, leading to the storage of triglycerides (TG) in adipocytes. Interestingly, when GF mice were fed a high-fat diet (HFD), they remained protected from developing obesity. [9,18] Additionally, Bäckhed at al., (2004) found that gut microbiota can affect fasting induced adipose factor (FIAF), a circulating lipoprotein lipase inhibitor that is usually suppressed in the gut epithelium but produced in adipose tissue and liver. Germ free mice have higher gut FIAF expression, however. Administering microorganisms from a normal mouse reduces this expression and results in higher triglyceride accumulation in adipose tissue. [19,20] In a study that was done on mice, researchers examined 5,088 bacterial 16S rRNA gene sequences from the cecal microbiota of genetically obese ob/ob mice, their lean ob/+ and wild-type siblings, as well as their ob/+ mothers, all of which were nourished the same diet high in polysaccharides. Compared to lean mice and irrespective of genetic relationship, ob/ob animals show a 50% decrease in Bacteroidetes abundance and a corresponding increase in Firmicutes. [21,22] These division-wide changes suggest that obesity influences gut microbiota diversity in this model and imply that intentional modification of the community structure could help control energy balance in obese individuals. [21] The same team of the previous study observed similar differences in the gut microbiota between lean and obese humans in their initial studies. It was discovered that

obese individuals had fewer Bacteroidetes and more Firmicutes compared to lean control subjects. Additionally, after 52 weeks of diet-induced weight loss, the ratio of Bacteroidetes to Firmicutes in the obese individuals shifted closer to that observed in lean individuals. [22,23] Collectively, the findings from both mice and humans indicate that obesity changes the composition of the gut microbiota. [22] Moreover, In an Iranian study, authors noted a significant rise in the F/B ratio in the obese group in comparison with the normal weight group ($p = 0.002$). While the abundance of and *Bifidobacterium* ($p = 0.049$) significantly declined, as BMI increased across the studied groups. [24] This suggests that adjusting the gut microbiota to achieve a lower Firmicutes/Bacteroidetes ratio might offer a new approach to managing obesity; however, on the contrary there are several studies reported no differences in the levels of Firmicutes and Bacteroidetes between obese and lean subjects, and in some instances, even found opposite association. [22] So, defining an "obese" microbiota is still not possible because of the numerous confounding factors, such as genetic variation, diet, and lifestyle, present in the human population. Moreover, it is probable that the same gut microbiota could have varying effects on obesity development within the diverse human population. [22]

2.0 Modulation of gut microbiota for obesity management

Multiple studies have demonstrated that the gut microbiota is crucial not only for host physiology but also in regulating obesity. These findings suggest that altering the gut microbiota through dietary interventions or other methods could offer benefits by restoring gut function and correcting the dysbiosis associated with obesity. [17]Diet induced weight loss is linked to enhanced gut bacterial gene richness and decreased chronic systematic inflammation. When patients with obesity followed a carb restricted or fat restricted low calorie diets, reported a reduction in

firmicutes and a rise in bacteriocides. [25] Diets with significant amount of proteins were linked to specific gut bacterial groups, including bacteriocides, while prevotella has been associated with fiber rich diets. Compared to other diets, the Mediterranean diet which promote the consumption of extra virgin olive oil, seafood, nuts, beans, veggies and fruits is considered the optimal diet to support a healthy intestinal bacterial composition. Moreover, physical exercise can alter the gut microbiota by increasing the amount of beneficial bacteria. [25] In addition to the previously mentioned methods, there are other approaches to modify a dysbiotic gut microbiota to achieve a healthier, more balanced profile. These methods include: (1) eliminating specific harmful strains with the use of antibiotics ("antimicrobial therapy") or bacteriophages ("phage therapy"), (2) administering live beneficial microbes known as "probiotics," or (3) transplanting entire communities of microbiota through "fecal microbiota transplantation".[26] In the following paragraphs, I will explore four different approaches to modulating the gut microbiota for obesity treatment.

2.1 Prebiotics

A prebiotic is defined as "a non-digestible food component that positively impacts the host's health by specifically promoting the growth and/or activity of certain bacteria in the colon, thereby enhancing overall well-being". [27] The prebiotics most frequently utilized in practice include fructooligosaccharides, galactooligosaccharides, lactulose, and non-digestible carbohydrates such as inulin, cellulose, resistant starches, hemicelluloses, gums, pectins as well as cyclodextrins (CDs). [9] Specifically, inulin-type fructans (ITF) and galactooligosaccharides (GOS) have been shown to increase the growth of Bifidobacteria and Lactobacilli, leading to significant alterations in the composition of the gut microbiota.[28] Prebiotic-rich diets have been

linked to lower food intake, body fat content, and weight increase, particularly in overweight and obese individuals. [28] Research has demonstrated that altering the microbiota through prebiotic consumption plays a crucial role in treating certain diseases and could be viewed as a possible focus for future therapeutic strategies. The positive effects of prebiotics are generally linked to: 1) promoting the growth of beneficial bacteria and increasing SCFA production which serve as the main energy source for the intestines, enhances barrier function, boosts resistance to inflammatory triggers and exert various metabolic effects on the host; 2) elevating the levels of certain beneficial species (like *Bifidobacterium*, which may help to correct gut dysbiosis; and 3) influencing lipid metabolism, potentially through the inhibition of lipogenic enzymes, leading to a reduction in the synthesis of lipoproteins and triglycerides. [1,27] Research in animals has shown compelling evidence that prebiotics can alter the composition of gut microbiota, leading to a reduction in metabolic endotoxemia and inflammation; however, in human studies, this association remains more debatable. Dewulf et al. demonstrated that consuming inulin-type fructan for three months led to changes in the intestinal microbiota and lipid metabolism in obese women.[29,30] As a result, the treatment was associated with a reduction in fat mass, serum LPS levels, and metabolites such as hippurate, lactate, and phosphatidylcholine. Lowering circulating LPS levels through the promotion of a healthy intestinal microbiota is a crucial factor in achieving reduced inflammation related to obesity and metabolic disorders. [30] Studies has indicated that prebiotics, particularly FOS and inulin, can decrease hunger and energy consumption by raising the levels of glucagon-like peptide (GLP-1) and peptide YY (PYY), due to the enhanced production of SCFAs. GLP-1 and PYY, are hormones that promote satiety and help regulate food intake. Soluble prebiotic fibers absorb water in the stomach, leading to greater stomach expansion, which is linked to delayed gastric emptying and an increased feeling of

fullness. Obese pre-menopausal women were evaluated for 120 days in a double blind placebo controlled trial. Two doses of yacon syrup , 0.29 g and 0.14 g fructooligosaccharides/kg/day were administered. The daily consumption of yacon syrup resulted in a considerable reduction in body weight, waits circumference and body mass index. [31] Overall, prebiotics help manage obesity by reducing the production of LPS through the modulation of gut microbiota, which in turn decreases low-grade inflammation and influences the endocannabinoid system. [9]

2.2 Probiotics

Probiotics are live microorganisms that have been demonstrated to improve host health when given in sufficient doses. Probiotics, whether they are colonizing or in transit, interact with the host in a number of ways. [32]These interactions include: (1) altering the functions of the endogenous microbiota, which influences how it interacts with the host and prevents pathogens from competing with it; (2) enhancing the function of the epithelial barrier by increasing the production of the intestinal mucus layer (3) altering the behavior of immune cells and cytokine profiles 4) diminishing adipocyte size by reducing fatty acid absorption and boosting genes involved in fatty acid oxidation. (5) Additional possible effect for probiotics is the decrease of chronic systematic inflammation of low intensity, which occurs with obesity. Collectively, these strategies can influence the structure of the gut microbiota, leading to the recovery of a "lean gut microbiota". [19] Also, probiotics affect appetite and energy homeostasis by increasing short chain fatty acids production. Probiotics promote the growth of Akkermansia muciniphila, leading to improved mucus thickness and intestinal barrier integrity.[28] The positive effect is coupled with a decrease in serum LPS levels and an enhancement in the metabolic profile; decrease in total cholesterol, LDL, TG levels and a raise in HDL cholesterol.

Additional possible effect for probiotics is the decrease of chronic systematic inflammation of low intensity, which occurs with obesity.[28] Probiotic therapies have been shown to diminish body weight growth and fat buildup in mouse models of obesity, outnumbering trials that found no change in weight or fat mass. [32] According to the literature cited, many probiotics whether used individually or in symbiotic combination have shown beneficial effects on obesity through mechanisms that are specific to certain species and strains such as modulation of the gut microbiota, reduction of insulin resistance, and enhanced satiety. Lactobacillus species (including L. Casei strain Shirota (LAB13), L. Gasseri, L. Rhamnosus, and L. Plantarum) and Bifidobacterium species (such as B. Infantis, B. Longum, and B. Breve B3) have been successfully used in solidified animal obesity models. These strains are preferred because of their low pathogenicity and weak antibiotic resistance. Also, certain Bifidobacterium and Lactobacillus spp. produce beneficial conjugated linoleic acid. CLA influences body weight via enhancing energy metabolism and lipolysis. [28] Such therapies resulted in lower weight gain and fat accumulation compared to placebo groups. However, more research is needed.

2.3 Synbiotics

The word “symbiotic” is used to refer to a mix of probiotic and prebiotic that works together and provide greater benefits that either alone. As the expression “symbiotic” implies the term “synergy”. Symbiotic combine probiotic and prebiotic properties to improve viability of probiotic in the gastrointestinal tract.[12] Symbiotic formulations consist of probiotic strains such as Lacbobacilli, Bifidobacteria spp., S. boulardii, and B. coagulans, as well as prebiotics such as fructooligosaccharides (FOS), GOS, and xyloseoligosaccharide (XOS), inulin, and prebiotics from natural sources such as chicory and yacon roots. [33] Supplementing with symbiotic has been

shown to improve waist and hip circumference, BMI and visceral fat area in overweight and obese subjects despite some inconsistent findings. [34] Symbiotic can affect the intestinal microbiota, reduce inflammation, and induce remission in IBD in addition to preventing traveler diarrhea and improving the overall quality of life in patients .[33]In a randomized placebo controlled clinical trial, 60 older patients with metabolic syndrome were randomly assigned to receive a synbiotic formula containing Lactobacillus plantarum PBS067, Lactobacillus acidophilus PBS066, and Lactobacillus reuteri PBS072 with active prebiotics or placebo for 60 days. [35] Active treatments resulted in substantial reductions in waist circumference, fasting plasma insulin, total cholesterol, high-density lipoprotein cholesterol, non-HDL-C, triglycerides (TG), low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and tumor necrosis markers over a 2-month period. [35]

2.4 Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is gaining prevalence as a method to modify gut microbiome structure in the context of various diseases. This procedure involves introducing intestinal microbiota from the stool of a healthy donor into the patient's gastrointestinal tract.[36] It is primarily used to treat gastrointestinal disorders caused by pathogenic or opportunistic microorganisms. Lately, there have been efforts to implement FMT as a treatment for conditions such as metabolic syndrome, diabetes, Crohn's disease, inflammatory bowel disease (IBD), Parkinson's disease, multiple sclerosis, psoriasis, anorexia nervosa, and Alzheimer's disease [7]. The primary routine application of FMT is in the treatment of Clostridium difficile (CD) infection, specifically for cases that do not respond to antibiotic therapy. This condition is primarily caused by significant gut microbiota dysbiosis, often resulting from multiple courses of

antibiotics. [37] FMT works by increasing gut microbiota diversity, resulting in a positive clinical outcome or even complete resolution in 80 to 90% of cases, with approximately 60% experiencing full remission within one month following the procedure. [37] Unlike other methods designed to modify the gut microbiota, fecal microbiota transplantation (FMT) involves transferring the entire, stable microbial community present in the feces of healthy donors to individuals suffering from a disease linked to an imbalanced microbiota. The primary objective of this technique is to restore the microbial balance and alleviate the symptoms associated with the disease. [26] In contrast to probiotics, which typically introduce only a limited number of microbial species into the host's gut, fecal microbiota transplantation (FMT) offers the advantage of transferring the complete microbial ecosystem, functioning as a whole "organ." Unlike other organ transplants, FMT is notably safe and does not provoke an immune response or rejection. [26] There are different delivery methods for the transplantation which includes oral capsules, nasal tube, nasogastric tube, nasoduedunal tube, nasojejunal tube and colonoscopy, transendoscoping enteral tubing or enema. [26] The justification for utilizing Fecal Microbiota Transplantation (FMT) as a method for weight loss is supported by two primary observations. As mentioned before, studies have suggested that the gut microbiota in obese individuals may promote greater energy storage compared to those in lean individuals, even when calorie intake is identical, though these findings have been doubted. [37] Second, it has been shown that transferring microbiota from obese humans or mice to germ-free recipients can lead to weight gain. This has led to the hypothesis that introducing FMT from lean donors into overweight or obese individuals might influence their weight, potentially offering a new strategy for weight management. However, this idea is still unproven and remains a topic of debate. [37]

3.0 Materials and methods:

3.1 Search strategy

An inclusive search was done throughout PubMed and Google search. The research question was asked using the PICO approach (population, intervention, control, outcome). Using the keywords: “probiotics” OR “prebiotic” OR “Synbiotics” AND “weight loss” and also “fecal microbiota transplantation” AND “weight loss” . The search was focused on randomized clinical studies that studies the effects of prebiotics, probiotic, symbiotic and fecal transplantation on weight loss in patients with obesity and overweight.

3.2 Eligibility criteria

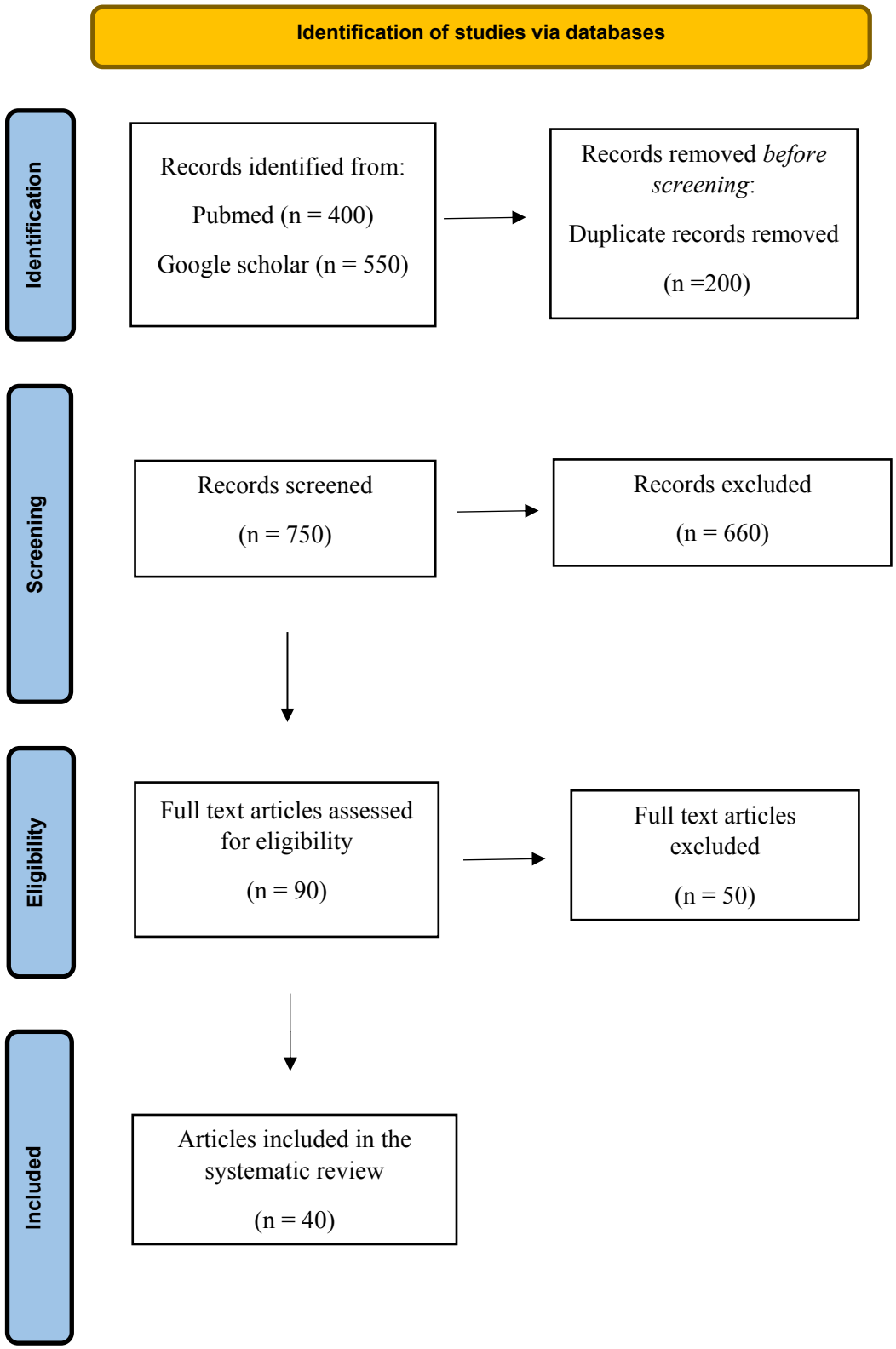
PICOS criteria was used to establish the included studies. I evaluated the title and the abstract of the article. (1) I mainly focused on randomized clinical trials that examined he effects of prebiotics, probiotics , symbiotic and fecal microbiota transplantation (2) Patients who are overweight or obese who BMI > or equal 25 kg/m2 and above 14 years with or without type 2 diabetes or any other disease (3) Randomized clinical trials that compared the effect of the previously mentioned interventions with placebo (4) Studies that reported weight (kg), BMI (kg/m2) and waist circumference as an outcome.

P: population	Adolescents with obesity or overweight 25 kg/m2 or more, aged 14 years old or above, with or without type 2 diabetes or any chronic disease.

I: Intervention	Supplementation of probiotic, symbiotic, prebiotic or oral capsules of fecal microbiota transplantation
C: Comparison	If any of the above-mentioned interventions are compared with placebo
O: Outcomes	Body weight (kg), waist circumference (cm) or Body mass index (kg/m2)

Exclusion criteria are the studies that included children, are not randomized clinical trial, any study that evaluated the effect of any of the interventions after an initial phase of dietary intervention, patients who are not overweight or obese and less than 14 years old.

4.1 Selection process



The PubMed and google scholar searches yielded 400 and 550 hits, respectively. Of the 950 articles, 200 were eliminated prior to screening. The remaining 750 studies were assessed for title and abstract, with 600 deemed irrelevant to my research. A total of 90 articles underwent full-text assessment. Of them, 40 met the selection criteria and are included in the systematic review.

4.2 Study characteristics

The following table provides the characteristics of the studies included in the systematic review and meta-analysis. I gathered, the author, year, country, population, intervention type and dosage and the outcome. The primary outcomes are the body weight (kg), waist circumference (cm) and the body mass index (kg/m2).

Table 1: characteristic of studies included

Author & country	**Design of the study**	**Participants**	**Intervention: Probiotic/prebiotic/symbiotic type and dosage**	**Placebo**	**Duration/ Period**	**Outcome**
Allegretti et al. 2020[38]	randomized, placebo-controlled, pilot study	22 obese patients	Fecal oral microbiota capsules (induction dose of 30 capsules at week 4 and maintenance dose of 12 capsules at week 8)	-	26 weeks	Body weight
Yu et al. 2020[39] America	double-blind randomized placebo-controlled pilot trial	24 adults with obesity and mild–moderate insulin resistance	Fecal microbiota transplantation (FMT)	Placebo	12-weeks	Weight Fat mass, HOMA-IR
Neto et al. 2023 [40] Brazil	Randomized, single-blind, placebo-	32 female patients (age range, 20–69	Fecal microbial transplantation	Sham procedure	1 year after the procedure	Hip circumference, fasting glucose, insulin, glycated hemoglobin

	controlled clinical trial	years) with class II obesity(BMI 30–40 kg/m2) and metabolic syndrome				
Leong et al. 2020 [41] New Zealand	This randomized, double-masked, placebo-controlled trial	87 adolescents aged 14 to 18 years with a BMI of 30 or more Mean [SD] age 17.2 [1.4] years)	Encapsulated fecal microbiome N= 42	Placebo	26 week follow up	BMI, waist circumference, total body fat %, total lean mass, fasting insulin, fasting glucose, HBA1c, systolic and diastolic blood pressure, HOMA-IR
Janczy et al. 2020[42] Poland	Prospective randomized, **single blinded trial.**	60 subjects with BMI ≥25 kg/m2, 56 (44 F and 12 M, mean age 40.8±14 years) Reduction diet was applied in all subjects	Synbiotic group	Placebo	12 weeks	BMI, body mass
Rabiei et al. 2015[43] Iran	Triple blind randomized controlled trial	46 volunteers from both sexes aged 25-70, with BMI≥ 25 kg/m2, who had at least three determinants of metabolic syndrome, were recruited	2 synbiotic capsules	Placebo	12 weeks	BMI, waist circumference, fat mass % , lean mass %, HC, systolic blood pressure, diastolic blood pressure.

Eslamparast et al. 2014[44] Iran	Randomised, double-blind, placebo-controlled pilot study	38 subjects with metabolic syndrome	Synbiotic capsules containing 200 million of seven strains of friendly bacteria plus fructo-oligosaccharide	Placebo	28 weeks	Fasting blood sugar, TAG, total CT, HDL, LDL, waist circumference, BMI.
Sergeev et al. 2020[45]	Placebo-controlled intervention clinical trial	Overweight and obese patients with a BMI of 33.5 kg/m2.	symbiotic	Placebo	3 months intervention	Body mass, Body Fat Mass, Body Fat, BMI, waist circumference, HbA1C (%), Body Lean Mass, BMC, Body Lean Mass.
Anggeraini et al. 2021[46] Indonesia	Randomized, double-blind placebo-controlled	40 participants with obesity (BMI of ≥25 kg/m2)	Synbiotic supplementation	Placebo	8 weeks	Body weight, BMI Fasting blood glucose
Kooshki et al. 2017[47] Iran	clinical double-blind trial study	43 overweight patients with type 2 diabetes	Synbiotic supplement containing 1.5×10^7 Bacillus coagulants and 100 mg Fructo-oligosaccharides	Placebo	8 weeks	BMI, weight, fasting blood sugar (mg/dL)
Lyon III et al. 2023[48] USA	Randomized, double-blind, placebo-controlled clinical trial	172 individuals aged 30 to 60 years with BMI of 25 to 34.9 kg/m2	Synbiotic v5 or v7	Placebo	12 weeks	BMI and body weight, body fat percentage, waist circumference, hip circumference, HDL, HOMA-IR, CRP

Chaiyasut et al. 2021[49] Thailand	Randomized double blind placebo-controlled trials	Thai obese adults (BMI _ 25 kg/m2), aged 18–65 years	Symbiotic (Lactobacillus paracasei, Bifidobacterium longum, Bifidobacterium breve, inulin, and fructooligosaccharide)	Placebo	12 weeks	Body weight, BMI, waist circumference, body fat %, muscles % , BMR, arm circumference, hip circumference, WHR, total CT, TG, LDL, HDL, FBS, IL-6 (pg/mL), IL-10 (pg/mL), IL-1_ (pg/mL), TNF-_ (pg/mL), hsCRP (ml/L), IGA, LPS
Oraphruek et al. 2023 [50] Thailand	A double-blind, placebo-controlled, randomized, parallel design	which 63 individuals aged 18–45 years having a body mass index (BMI) between 23 and 30 kg/m2	synbiotic group consumed a daily dose of 37 _ 109 colony-forming units (CFU) of a unique blend of seven different probiotics, along with 2 g of fructooligosaccharides	Placebo	12 weeks	Body weight, waist circumference, BMI, body fat %, FBG, HDL, LDL, TG, total cholesterol
Batu et al. 2021[51] Turkey	Randomized, placebo-controlled and single-blind	Sixty-one not compliant with diet and exercise recommendations, sedentary obese women (BMI: 30-39.9 kg/m2) aged between 18 and 48.	Synbiotic (3x109 cfu *Bifidobacterium lactis, Lactobacillus acidophilus, Bifidobacterium longum, Bifidobacterium bifidum,* 159.45 mg Fructooligosaccharide ,	Placebo	6 weeks	Body Weight, BMI, Waist Circumference, hip circumference, waist to hip ratio, body fat ratio

Hadi et al. 2019 [52] Iran	randomized double-blind, placebo-controlled trial	60 adults with overweight or obesity	Synbiotics (n =30) in form of a 500mg capsule (containing Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum plus inulin).	Placebo	8 weeks	Body weight, BMI, waist circumference, TG, LDL, HDL, systolic blood pressure, diastolic bood pressure, fasting insulin stress, depression, anxiety
Jun Oh et al. 2023 [53] korea	Randomized, double-blind, placebo-controlled clinical trial	Overweight individuals (body mass index ≥25 kg/m2 aged 20-60 years old	DW2010 (2.0 g/day, 1.0×10^{10} CFU)	Placebo	12 weeks	DW2010 Group: Body weight, BMI, visceral fat area, body fat, waist circumference
Higashikawa et al. 2016 [54] Japan	double-blind, randomized, placebo-controlled study	62 subjects (20–70 years of age, BMI 25–30 kg/m2)	living LP28, heat-killed LP28 probiotic	Placebo	12 weeks	BMI (kg/m2), body fat %, waist circumference, body fat mass,
Mobini et al. 2016 [55] Sweden	A double-blind trial,	45 patients with type 2 diabetes, age 50–75 years; abdominal obesity (women: waist >80 cm; men: waist >94 cm); BMI: 25-45 kg/m2	3 groups: placebo or a low (108 CFU/d) or high dose (1010 CFU/d) of L. reuteri DSM 17938	Placebo	12 weeks	Waist circumference, BMI, weight

Ranjbar et al. 2023 [56] Iran	Double-blind randomized clinical trial study	66 obese patients with BMI in the range of 30–40 kg/m2	probiotic 2 capsules per day (*Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus casei and Bifidobacterium langum*) N= 25	Placebo	3 months	Weight, BMI, hip circumference, HC, Fasting blood glucose, insulin, triglyceride, HDL, LDL, AST, ALT, CRP, systolic blood pressure, diastolic blood pressure.
Verma et al. 2021 [57] USA	Randomized, double blind, placebo-controlled, 12-week pilot clinical	15 Adolescents with severe obesity	Oral probiotic 'VisbiomeR'	Placebo	12 weeks	Fasting insulin, weight, BMI, HOMA-IR,
Sohn et al. 2022 [58] Korea	randomized, double-blind, placebo-controlled, clinical trial	81 adults with a body mass index of 25–30 kg/m2	A diet including 4×10^9 colony-forming unit of LPK (*Lactobacillus plantarum* K50)	Placebo	12 weeks	Waist circumference, BMI, body weight, fat mass, lean mass, body fat %, TAT, VAT, SAT, total cholesterol, HDL, LDL, CRP, insulin, glucose, glucagon, SBP, DBP, free fatty acid, leptin, creatinine, AST, ALT.
Madempudi et al. 2019 [59] India	A double blind, randomized, placebo-controlled study	79 eligible subjects have type 2 diabetes (18–65 years, on stable metformin therapy)	Multi-strain probiotic: UB0316 (*L. salivarius* UBLS22, *L. casei* UBLC42, *L. plantarum* UBLP40, *L. acidophilus* UBLA34, *B. breve* UBBr01, *B. coagulans* Unique IS2, 5 billion CFU each and fructo-oligosaccharides, 100 mg)	Placebo	12 weeks	HOMA_IR, weight, HBA1C, fasting blood glucose, TC, TG, HDL, LDL, insulin

Czajeczny et al. 2020 [60] Poland	Randomized, single-blind, placebo-control design	53 females aged 19–33 were enrolled, and 38 completed the trial	*Bifidobacterium lactis* BS01 (2 × 109 CFU) and *Lactobacillus acidophilus LA02* (2 × 109 CFU) bacteria.	Placebo	6 weeks	weight, Arm skinfold fat (mm), WC, body fay %, BMI, WHR,
Song et al. 2020 [61] Korea	Double-blind, placebo-controlled, randomized clinical trial	50 healthy obese men and women with body mass index over 25 kg/m2	Probiotic capsules , GP2 (Cell Biotech Co. Ltd., Gimpo, Republic of Korea), contained a formulation consisting of B. breve CBT BR3 isolated from Korean infant feces (15 billion viable cells/ 2 capsules), L. plantarum CBT LP3 isolated from Korean fermented vegetable product kimchi (15 billion viable cells/2 capsules), fructo-oligosaccharide, and magnesium stearate.	Placebo	12 weeks	Weight, BMI, waist circumference, Total fat area, HC, Visceral fat area, V/S ratio Systolic BP (mmHg) Diastolic BP (mmHg) Pulse rate (/min), fat mass,fat percentage
Micheal et al. 2018 [62] Bulgaria	block-randomized, parallel, double-blind, single-centre, placebo-controlled superiority study	220 participants (30 to 65 years old) with BMI 25–34.9 kg/m2had a waist circumference > 89 cm (women) or	Lab4P probiotic (50 billion/day)	Placebo	6 months	Body weight, BMI, WC, waist to hip ratio, LDL CT

		> 100 cm (men);				
Mo et al. 2022[63] Korea	Randomized, double-blind, placebo-controlled study	72 individuals with overweight	Probiotic groups consumed 1×10^{10} colony-forming units of HY7601 and KY1032	Placebo	12 weeks	Body weight, BMI, waist circumference, Hip circumference, percent body fat, body fat mass, lean body mass, visceral fat area, total CT, LDL, HDL, TG, leptin, adiponectin, CRP.
Jung et al. 2013 [64]	Randomized double blind clinical trial	62 Overweight and obese Men and non-pregnant women between 19-60 years (BMI) ≥ 23 kg/m2 and fasting blood sugar (FBS) ≥ 100 mg/dL	BNR17 capsules (probiotic) were composed of 10^{10} cfu of Lb. gasseri BNR17 and filler powder (50% trehalose, 25% skim milk, and 25% fructooligosaccharide)	Placebo	12 weeks	Body weight, BMI, waist circumference, WHR, hip circumference
Cho et al. 2022[65] Korea	Randomized, Multicenter, Double-Blind, Placebo-Controlled Study	100 healthy obese and overweight subjects aged 19–65 years with a body mass index (BMI) between 25 and 31.9 kg/m2 were recruited	MED-02 ($5 * 10^9$ CFU/day)	Placebo	12 weeks	BMI, waist, hip, waist to hip ratio, lean body mass, visceral fat area, subcutaneous fat area, Total abdominal fat area (cm2), Visceral-to-subcutaneous fat ratio, total cholesterol, HDL, LDL, TG, Adiponectin, leptin, CRP

Lim et al. 2020 [66] Korea	Randomized, double-blind, placebo-controlled, clinical trial	114 adults with a body mass index (BMI) ≥25 kg/2	5×109 colony forming units of CJLS03/allocation	Placebo	12 weeks	Body fat mass, BMI, WC, weight
Minami et al 2015 [67] Japan	randomised, double-blind, placebo-controlled trial	52 adults whose BMI (24 to 30 kg/m2) and age (40 to 69 years)	B-3 capsule (approximately 5 × 10^{10} colony-forming units of B-3/d) daily	Placebo	12 weeks	Body weight, BMI, waist to hip ratio, fat mass, fat percentage, muscle mass, fasting blood glucose, HBA1C, insulin, glycoalbumin, 1,5-Anyhdroglucitol, AST, ALP, ALT, total bilirubin, hCRP, γ-GTP.
Kim et al., 2018 [68] Korea	randomized, double-blind, placebo-controlled trial	90 volunteers aged 20–75 years with body mass index (BMI) from 25 to 35 kg/m2	low-dose BNR (BNR-L, 109 CFU/day), or high-dose BNR (BNR-H, 1010 CFU/day)	Placebo	12 weeks	Body weight, WC, BMI
Gomes et al. 2017 [69] Portugal	randomized, double-blind, placebo-controlled, twoarm, parallel-group study	women with excess weight or obesity and were 20 to 59 years old with a BMI (in kg/m2) from 24.9 to 40	probiotic mix (Lactobacillus acidophilus and casei; Lactococcus lactis; Bifidobacterium bifidum and lactis; 2 3 1010 colony-forming units/day) (n = 21) -four sachets daily before breakfast	Placebo	8 weeks	Other outcomes: , weight, WC, BMI, body fat, fat mass, fat fre mass (kg) & %, waist to hip ratio, HBA1C, total cholesterol, LDL, HDL, TG
Szulinska et al. 2018 [70] Poland	12-week single-center randomized clinical trial	A total of 81 obese Caucasian postmenopausal women participated in the trial	3 groups: - a low dose (LD) (2.5 × 109 colony forming units (CFU) per day)	Placebo	12 weeks	Body weight, Fat (kg), BMI, waist HOMA-IR, visceral fat, subcutaneous fat, uric acid, LDL

		aged 45–70 years whose abdominal obesity-related waist circumference >80 cm	a high dose (HD) (1 × 1010 CFU per day) of lyophilisate powder containing live multispecies probiotic bacteria			
Gobel et al. 2012 [71] Denmark	A double-blind placebo-controlled trial	50 adolescents with obesity	Ls-33 (10^{10} CFU) N=27	Placebo N= 23	12 weeks	HOMA-IR, body fat %, waist to hip ratio, BMI, height, skin folds, systolic and diastolic blood pressure, CRP, IL-6, TNF-a,FC, FBG, RI, TG, TC, LDL, HDL
Sanchez et al. 2014 [72] Switzerland	A double-blind, placebo-controlled, randomised trial	Obese men and women age between 18 and 55 years; BMI between 29 and 41 kg/m^2	LPR formulation (1·6 * 108 colony-forming units of LPR/capsule with oligofructose and inulin).	Placebo	24 weeks	Body weight, fat mass
Uebelhack Et al. 2019 [73] Germany	A double-blind, randomized, placebo-controlled trial	108 subjects (BMI between 25 and 35 kg/m2)	2 capsules low-dose or the high-dose IQP-AE-103group	Placebo	12 weeks	Body weight, body fat, waist and hip circumference, CT levels, feeling of hunger
Canfora et al. 2017 [74] Germany	A double-blinded, placebo-controlled, parallel intervention study	44 overweight or obese (body mass index, 28–40 kg/m^2) prediabetic men and women (ages, 45–70 y)	Prebiotic 15 g Galacto-olisaccharides	Placebo	12 weeks	BMI, body weight, fasting insulin, body fat, lean mass, visceral fat, body fat percentage, glucose, free glycerol, FFA, leptin, glp1, PYY, LBP, pg/mL, IL6, pg/mL, IL8, pg/mL, TNF-a, pg/mL
Hess et al. 2019[75] Denmark	Randomised, placebo-controlled, double-blinded,	116 overweight or obese participants. between	Prebiotic 10 g inulin plus 10 g resistant maltodextrin	Placebo supplementation through 400 mL	12 weeks	Body weight, BMI, waist circumference, HOMA-IR, SBP, DBS

	parallel interventio n trial	18 and 60 years, have a BMI of 28– 45 kg/m2 and have blood haemoglobi n (Hgb) concentrati on above 7.0 mmol/L		of milk a day		
Hiel et al. 2020[76] Belgium	A randomized , single-blinded, multicentric , placebo-controlled trial	150 obese patients BMI >30 kg/ m2, aged from 18 to 65 years	Prebiotic received 16 g/d native inulin coupled to dietary advice to consume inulin-rich versus-poor vegetables for 3 months with dietary energy restriction	Placebo	3 months	Body weight, BMI, waist, HOMA-IR, waist to hip ratio, DBP, SBP, AST, fat mass
Parnell et al. 2009 [77]	A randomized , double-blind, placebo-controlled trial	48 otherwise healthy adults with a body mass index (in kg/m2) > 25	Prebiotic Received 21 g oligo fructose/d	Placebo	12 weeks	Glucose, weight, insulin

5.0 Systematic review

5.1 The effect of microbiota on FMT

5.1.1 The Effects of Fecal microbiota modulation on Body weight and BMI

Four randomized controlled trial were considered for fecal microbiota transplantation; in 3 studies [38,39,41] patients were given oral capsules and in one study [40] the prepared fecal microbiota solution was infused directly to the upper small intestine. Allegretti et al. [38] conducted a double-

blind trial on 22 obese patients (BMI more than or equal to 25 kg/m2) without diabetes, non-alcoholic steatohepatitis or metabolic syndrome. Participants were randomly allocated to either receive FMT capsules or placebo capsules and patients were monitored up to 26 weeks. It was found that FMT capsules were safe but did not decrease BMI in obese patients, no significant changes were observed in mean BMI at week 12 in either group.

In the study of Yu et al.[39] 24 adults aged between 25 and 60 years with obesity and low to moderate insulin resistance were randomly allocated to receive either oral FMT from healthy lean donors versus placebo capsules for 6 weeks, no statistically significant differences between the FMT and placebo group in body weight or others metabolic markers in adults with obesity and without diabetes.

Female patients with obesity class I or II, aged between 20 and 69 years with metabolic syndrome were selected for a randomized single blind placebo controlled clinical trial in the study of Neto et al.[40] 32 females were split into 8 groups of four patients each and in each group, two patients were randomly assigned to undergoes FMT and the other two patients received saline solution. There were no significant differences in body weight (94.12 + 8.27 kg vs 89.29 + 5.70 kg, P = 0.867), or BMI (36.69 + 2.94 kg/m2 vs 35.74 + 2.22 kg/m2 , P = 0.719) between the 2 studied groups after one year.

Leong et al.[41] researches did a randomized double masked placebo-controlled trial on adolescents aged 14 – 18 years with a BMI of 30 kg/m2 or more with 26 weeks follow ups with an intervention of oral fecal microbiome from 4 healthy lean donors or saline placebo. Results showed no effect of FMT on BMI standard deviation score at 6 weeks (adjusted mean difference [aMD] −0.026; 95% CI −0.074, 0.022).

5.1.2 The effect of FMT on waist circumference

Only Neto et al.[40] assessed the effect of FMT on waist circumference did not find any substantial effect in relative to the placebo group. The three other studies[39,40,42] did not report the effect of FMT on waist circumference.

5.2 The effect of symbiotic

5.2.1 The Effect of synbiotic on body weight and BMI

Recent research has investigated the effects of synbiotics on body weight, 8 articles analyzed the effect of symbiotic on body weight [42,45,46,48,49,50,51,52] and 11 articles on BMI [42,43,44,45,46,47,48,49,50,51,52] in patients with obesity and overweight. The evidence of these randomized placebo-controlled trials presents mixed outcomes. Janczy et al.[42] found significant reductions in body weight and BMI in comparison to baseline parameters $P< 0.0001$, the symbiotic and placebo groups (5.6 kg and 5.8 kg) respectively, but the difference was not statistically significant. Also, in Rabieh et al.[43] which is a triple blind study found that BMI and waist circumference were considerably lowered in both group (symbiotic and placebo) at weeks 6 and 12. It is important to mention that in this study participants in the placebo group no longer experienced further weight loss after 6 weeks, while patients in the symbiotic group continued to lose weight significantly until week 12 of the study and this effect may be explained by the impact of symbiotic on appetite. All the participants in both groups followed a weight loss plan. Only synbitoic group showed a substantial drop in these parameters between weeks 6 and 12 ($p<0.05$). However, some studies including Eslamparast et al.[44], serveeg et al.[45], Batu et al., and oraphruek et al.[50], that showed no statistical difference in BMI and wait circumference, and

weight between symbiotic and placebo groups. On the contrary, Anggeraini et al.[46] showed insignificant elevation in body weight and BMI in obese patients after 8 weeks of symbiotic supplementation (increase by 0.63 kg) while a significant increase in the placebo group by 2.375 kg ($p<0.0001$) and 4 weeks after cessation of placebo in 1 kg ($p= 0.099$). Weight and BMI change of (-2.88, -0.41, $p=0.01$) and (-0.71, -0.17) respectively in the intervention and placebo group were seen in the study of Kooshki et al.[47].The reduction symbiotic groups V5 and V7 groups is statistically significant compared with the change in placebo group ($p<0.0001$) and a decrease in body weight with V5 and V7 ($p<0.0001$) lyon III et al.[48]. In chaysut et al.[49] study, a notable change was seen in the symbiotic group after 12 weeks of supplementation in body weight, BMI, and body fat percentage. Substantial reduction in body weight ($p=0.03$) were seen in the study of Hadi et al.[52] in the symbiotic group compared to the placebo; however, no significant effect on BMI and WC ($p<0.05$).

5.2.2 Effect of symbiotic on waist circumference:

Eight studies analyzed the effects of symbiotic on waist circumference. In the study of Batu et al.[52] the consumption of synbiotics for 12 weeks resulted in a significant decrease in waist circumference ($p = 0.004$); however, when compared to the placebo groups, differences in waist circumference were insignificant. Rabieh et al. [43] chaiysut et al.[49] and lyon III et al.[48] found changes in the waist circumference of the symbiotic group. While 4 other studies [44,45,50,52] demonstrated no changes.

5.3 The effect of probiotic

5.3.1 The effect of probiotic on body weight and BMI

The evaluated research show that probiotic supplementation has various effects on body weight and BMI among individuals with obesity and overweight. Jun OH et al.[53] found that the probiotic group (DW2010) a small drop in weight (-1.19 kg) and BMI (-0.43 kg/m2) over 12 weeks, but results were not substantially different from the placebo group. Higashikawa et al. [54] discovered that heat killed lactobacillus plantarum (LP28) decreased BMI (-0.45 kg/m2) compared to placebo. A Swedish trial by Mobini et al. [55] stated that high doses lactobacillus reuteri supplementation lowered BMI (-0.2 kg/m2) but without statistical significance and no effect on weight. In Ranjbar et al. [56] randomized controlled study, it was reported that both patients who received the probiotic (*Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus casei and Bifidobacterium langum*) and who received the placebo noticed a reduction of their BMI, WC and body weight after a 3 month trial, but the reduction amount's mean was higher in the probiotic group. Madempudi et al. [59] observed that multi-strain probiotics: UB0316 *(*L. salivarius *UBLS22,* L. casei *UBLC42,* L. plantarum *UBLP40,* L. acidophilus *UBLA34,* B. bre ve *UBBr01, and* B. coagulans *Unique IS2, 30 billion CFU and fructo-oligosaccharide, 100 mg)* significantly reduced weight in diabetic patients in comparison with placebo. Mo et al.[63] discovered that HY7601 and KY1032 ($1*10^{10}$) resulted in significant reductions in body weight (0.93 kg vs 0.47 kg, $p < 0.001$) and BMI (0.32 kg/m2 vs. 0.15 kg/m2, $p = 0.007$) in the probiotic group compared to placebo. In the randomized double blind clinical trial of Jung et al. [64] a reduction in body weight (-1.1 kg) was noted in the BNR-H probiotic group compared to the placebo. Substantial decrease in weight (-0.98) in the probiotic group were seen in the study of

Gomes et al. [69] . Sanchez et al.[72] provided evidence that women in the probiotic group (LPR) lost significantly more weight after 12 weeks compared to the placebo group (P=0.02), with an average weight loss of 4.2 kg versus 3.4 kg. Uebelhack et al.[73] observed that high-dose of IQP-AE-103 group had a significantly greater weight loss compared with the placebo (5.03 ± 2.50 kg vs. 0.98 ± 2.06 kg, respectively; $p < 0.001$) and the low-dose group (3.01 ± 2.19 kg; $p = 0.001$). In Michael et al.[62] trial which is 9 months randomized parallel double-blind placebo-controlled trial in which participant received Lab4P probiotic including lactobacilli and bifidobacterial (50 billion cfu/ day), while subject following their normal diet and lifestyle across the 9-month trial, a substantial reduction in body weight (3.16 kg, 95% CI 3.94, 2.38, $p<0.0001$) was noticed in the probiotic group. In cho et al. [65], after 12 weeks intake of MED-02 which contains 2 probiotic strains, (Limosilactobacillus fermentum MG4231 and MG4244) showed a significant decrease in body weight (-2.06 kg vs. -1.22kg; $p= 0.041$) in the MED-02 group compared to the placebo. Czajeczny et al.[60] did not observed any noticeable variations in body weight and BMI between the placebo and supplemented groups. However; no changes were seen in BMI and body weight after 12 weeks of consuming 5×109 colony forming units of the probiotic CJLS03 according to lim et al.[66] . When subject consumed the probiotic VisbiomeR in the randomized double- blind study of verma et al. [57] weight and BMI (mean ± SD) were unchanged in the treatment group (-1.07 ± 6.1 kg and -0.3 ± 2.2 kg/m 2 respectively) in relation to the placebo group (3.9 ± 5.1 kg, 1.0 ± 1.6 kg/m 2), but not significantly ($p = 0.12$ for weight and 0.38 for BMI). Minami et al.[68] found no major changes in weight and BMI between groups.

Also, other investigations, such as those conducted by Sohn et al.[58], kim et al.[68] , Gobel et al.[71] didn't find change in weight and BMI. Overall, data suggests that probiotic may cause modest

weight and BMI reductions but the extent of these benefits differs between bacterial strains and populations.

5.3.2 The Effect of probiotics on waist circumference:

Several studies showed that probiotic supplementation resulted in considerable reductions in waist circumference. Jun Oh et al.[53] found a drop in WC (−1.10 cm) in the DW2010 probiotic group and similar decreases in the placebo group, but not statistically significant. Higashikawa et al.[54] found a substantial drop in WC (−2.84 cm) in the heat-killed LP28 group. Ranjbar et al.[56] showed evidence that the probiotic group experienced a substantial reduction in WC (−5.3 cm) compared to the placebo. In a study by Song et al.[61], participants who consumed Bifidobacterium breve and Lactobacillus plantarum experienced a substantial reduction in WC (−1.88 cm, $p = 0.049$). Mo et al.[63] revealed that reduction in WC (-0.41 cm vs. +1.31) in the probiotic and placebo group respectively. In Michael et al a substantial reduction in waist circumference (2.58 cm, 95% CI 3.23, 1.94, $p < 0.0001$) between the groups. An intake of 5×10^9 colony forming units of CJLS03 probiotic for 12 weeks showed 0.8 cm reduction in waist circumference than in the placebo group ($p= 0.013$) in Lim et al.[66] study. In Miami et al.[67] randomized controlled study, the wait circumference was a bit lower in the B-3 group in relative to the placebo group even though participant were asked not to change in their dietary habits. Szulinska et al.[70] illustrated that a high dose intake of the probiotic (1 × 1010 CFU per day) of lyophilisate powder containing live multispecies probiotic bacteria lowered waist circumference by 1.7% ($p = 0.0199$, SMD = −0.54). In kim et al.[68] individuals when consumed lactobacillus gasseri BNR17 which is a probiotic strain isolated from human breast milk, Waist circumference were

significantly decreased in both the BNR-low and BNL-high groups (P = .045 and .012, respectively) compared with the baseline values, but not in the placebo group.

On the other hand, Mobini et al.[55] and Sohn et al.[58], Gobel et al.[71], sanchez et al.[72] and Jung et al.[64] exhibited no significant difference in WC between the probiotic and placebo groups.

5.4 The effect of prebiotic

5.4.1 The Effect of prebiotic on body weight and BMI:

Four studies investigated the impact of prebiotic on body weight and BMI. Canfora et al.[74] found that taking 15 g/day of oligosaccharides (GOS) resulted in no noticeable weight reduction or changes in BMI after 12 weeks, with the two group, placebo and GOS gaining a bit of weight. Similarly, Hess et al.[75] concluded that subjects who consumed 10 g inulin and 10 g resistant maltodextrin coupled with a calorie restricted diet lost weight at the same rate as the placebo group with no noteworthy differences. Hiel et al.[76] reflected that consuming 16 g of inulin daily for 3 months resulted in significant weight loss (-2.7 kg) and BMI decrease (-1.0 kg/m2) compared to placebo group. In parnel at al.[77] study, participants who received 21 g of oligofructose per day for 12 weeks, noticed a reduction in body weight of 1.03 ±0.43 kg with oligofructose supplementation, whereas the control group experienced an increase in body weight of 0.45 ± 0.31 kg over 12 weeks ($P = 0.01$).

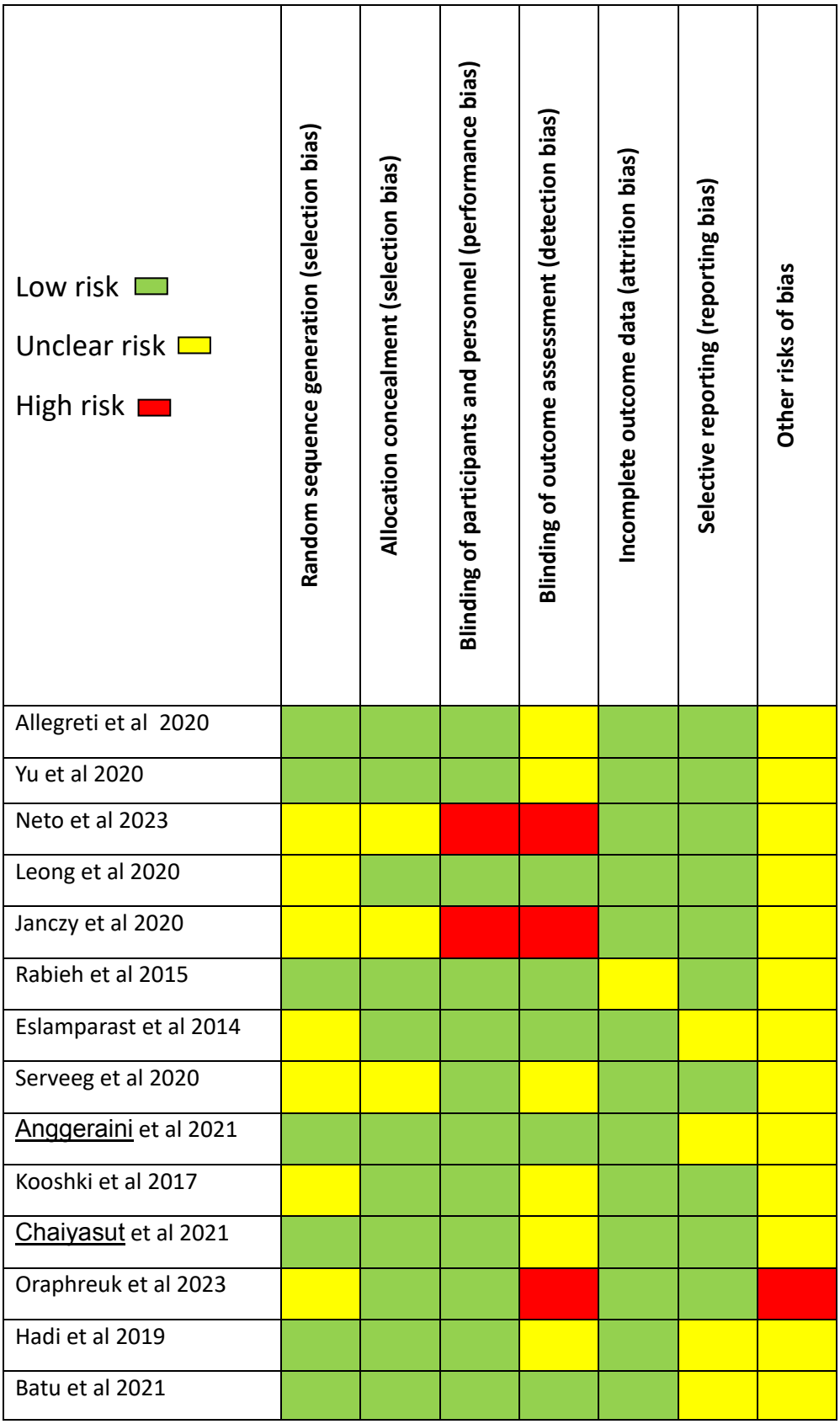
5.4.2 The effect of prebiotic on waist circumference:

Prebiotics reduce waist circumference (WC) more consistently across studies. In Hess et al.[75] both the fiber and placebo groups recognized significant reductions in WC over 12 weeks, with the fiber group demonstrating a significantly higher decrease (-5.7 cm) than the placebo (-5.4

cm). Hiel et al.[76] found that the prebiotic group experienced a −2.2 cm drop in waist circumference following 3 months of inulin intake, compared to −2.6 cm in the placebo group. Although both studies reported significant reductions, the additional effect of prebiotics compared to placebo on waist circumference was minor, indicating that, while prebiotics may help with waist circumference reduction, dietary interventions are equally important.

6.0 Quality assessment

The quality of the randomized controlled trials included in this review was assessed using the Cochrane Risk Assessment Tool, which examines six critical parameters. In regards to random sequencing, it was unclear in 15 studies and 25 low risks of bias. The allocation concealment or selection bias was in low risk for 27 articles and unclear for 12. As for the blinding of outcome personnel, the risk of bias was unclear for 20 articles, low risk for 31 and high risk for 4. 21 articles had unclear risk for blinding of outcome assessment, 7 articles high risk and 12 for low risk. Most of the articles had low risk of incomplete outcome data except for 7 who had unclear risk and 3 for high risk. Reporting bias was considered low for 27 articles, 8 in unclear risk, 5 in the high-risk category.


Low risk
Unclear risk
High risk
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other risks of bias
Allegreti et al 2020
Yu et al 2020
Neto et al 2023
Leong et al 2020
Janczy et al 2020
Rabieh et al 2015
Eslamparast et al 2014
Serveeg et al 2020
Anggeraini et al 2021
Kooshki et al 2017
Chaiyasut et al 2021
Oraphreuk et al 2023
Hadi et al 2019
Batu et al 2021

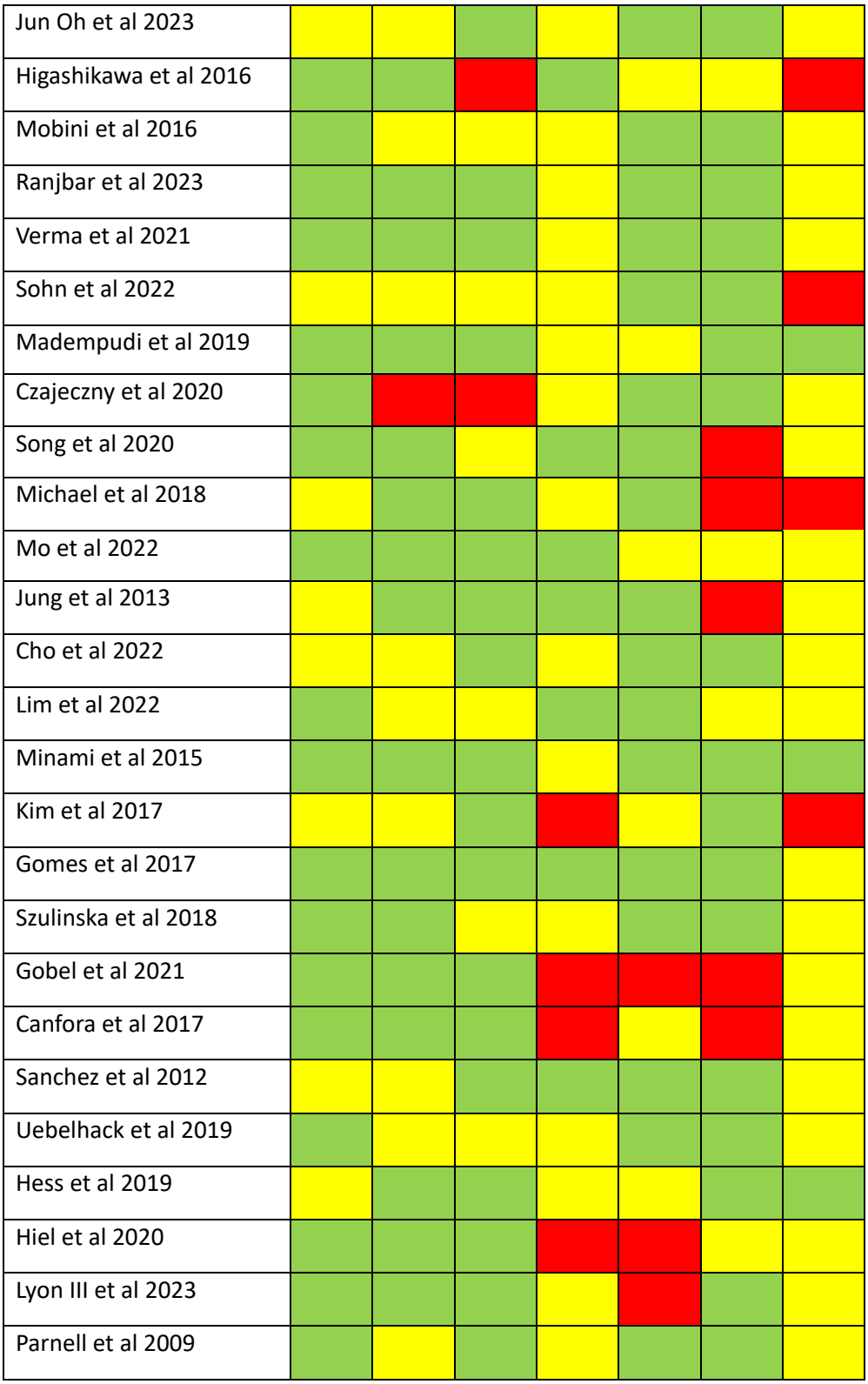


Table 2. Quality assessment for the randomized trials. Evaluation of risk as low in green, as high in red, and as unclear in yellow.

7.0 Discussion

The results of this systematic review indicates that fecal microbiota transplantation did not affect the BMI, body weight and waist circumference in individuals with obesity or overweight. However, 5 out of 11 articles from the synbiotic intervention showed that symbiotic might have benefits on body weight or BMI compared to placebo specifically the symbiotic that consisted of Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum, Lactobacillus bulgaricus, FOS (Fructooligosaccharide - Prebiotic), Magnesium stearate (source: mineral and vegetable), Vegetable capsule (hydroxypropyl methyl cellulose) TVC: 200 million CFU TVC: 2 × 108 CFU. Also, in research by hadi et al, 500mg capsule (containing Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum along with inulin, demonstrated positive effects. Additionally, in the study of chaysut et al, participant consumed (Lactobacillus paracasei, Bifidobacterium longum, Bifidobacterium breve, inulin, and fructooligosaccharide) and showed beneficial effects. Four out of eight studies showed a reduction in waist circumference in comparison with the placebo group. Most of the articles in the probiotic showed a positive effect however others did not. The inconsistent results regarding the probiotic intervention may indicate that while particular probiotic strains may have potential benefits in weight and control, their general efficacy can vary greatly depending on factors such as the formulations, dosage, research duration and the characteristic of participants. This emphasizes the need for additional research to better understand the conditions in which probiotics can effectively aid in weight management in individuals with obesity and overweight. Prebiotic studies didn't have significant effects on weight and BMI except for one study parnel et al.[78] which indicated a decrease in body weight, but some studies showed that prebiotic may have an impact on waist circumference.

Some of the limitations of the review is that in most of the included studies which provided notable improvements for reducing weight and body measurements (BMI and waist circumference), the interventions (probiotic, prebiotic and symbiotic supplementation) were given alongside with other weight loss approaches such as calorie restriction, low calorie diet or increase in physical activity. These methods are previously known to reduce weight making it difficult to link weight or body measurement entirely to probiotics. As a results, the real effect of the strains applied in the trials may be biased since the impact of diet or exercise was not distinct from the intervention's effect. Also, the studies discussed in this systematic review used various types and dosages for probiotic, prebiotics and synbiotics. This leads to heterogeneity between studies, different bacterial strains may have varied impacts on obesity and metabolism. Moreover, there were only four articles for the FMT and prebiotics, limiting the opportunity to draw firm conclusion about how effective these intervention for managing obesity. More future studies are needed to focus on these two interventions to provide clearer evidence. However; it is important to mention that all the studies included are randomized clinical trial (single, double and triple blind) and RCT is considered the gold standard for clinical research. Furthermore, including 40 studies provides an extensive overview of the present evidence and can offer major insights into the efficiency of microbiome therapies, despite the existing limitations.

8.0 Conclusion

This systematic review included 41 articles and demonstrated that probiotics and symbiotic may promote weight loss along with calorie restriction and physical activity. However more future research is needed to asses the effects of fecal microbiota intervention, symbiotic, prebiotic and probiotic on obesity management. More specific recommendation needed in terms of strains, dosage, duration. Future trials that do not include weight loss interventions, such as dietary adjustments or fitness programs, might be advantageous in precisely assessing the direct benefits of specific strains.

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