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REVIEW

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Associations between the gut microbiome and metabolic, inflammatory, and appetitive effects of sleeve gastrectomy

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Summary

The complex and multifactorial etiology of obesity creates challenges for its effective long-term management. Increasingly, the gut microbiome is reported to play a key role in the maintenance of host health and wellbeing, with its dysregulation associated with chronic diseases such as obesity. The gut microbiome is hypothesized to contribute to obesity development and pathogenesis via several pathways involving food digestion, energy harvest and storage, production of metabolites influencing satiety, maintenance of gut barrier integrity, and bile acid metabolism. Moreover, the gut microbiome likely contributes to the metabolic, inflammatory, and satiety benefits and sustained weight-loss effects following bariatric procedures such as sleeve gastrectomy. While the field of gut microbiome research in relation to obesity and sleeve gastrectomy outcomes is largely in its infancy, the gut microbiome nonetheless holds great potential for understanding some of the mechanisms behind sleeve gastrectomy outcomes as well as for optimizing post-surgery benefits. This review will explore the current literature within the field as well as discuss the current limitations, including the small sample size, variability in methodological approaches, and lack of associative data, which need to be addressed in future studies.

KEYWORDS
gut microbiome, obesity, sleeve gastrectomy

1 | INTRODUCTION

The incidence of obesity has tripled since 1975 and now accounts for over 1.9 billion adults worldwide.[1] The WHO defines obesity as the abnormal or excessive fat accumulation, which is commonly diagnosed in adults with a body mass index (BMI) ≥ 30 kg/m^2. In addition, obesity is associated with several non-communicable chronic diseases, including type 2 diabetes (T2D), cardiovascular disorders, non-alcoholic fatty liver disease (NAFLD), and colon cancer.[2] Unlike lifestyle interventions, bariatric surgery promotes sustained weight loss and attendant improvements in the dysmetabolic sequelae of obesity

Abbreviations: 5-HT, 5-hydroxytryptamine; BA, bile acid; BMI, body mass index; CA7S, cholic acid-7-sulfate; CR, calorie restriction; FMT, fecal microbial transplant; FXR, Farnesoid X receptor; GABA, gamma-aminobutyric acid; GF, germ free; GIT, gastrointestinal tract; GLP-1, glucagon-like peptide 1; GM, gut microbiome; HFD, high-fat diet; HIF-2α, hypoxia-inducible factor 2α; KO, knockout; LCA, lithocholic acid; LPS, lipopolysaccharide; LSD, liver shrinking diet; MAIT, mucosal-associated invariant T; NAFLD, non-alcoholic fatty liver disease; SCFAs, short-chain fatty acids; SG, sleeve gastrectomy; T2D, type 2 diabetes; TGR-5, Takeda G-protein-coupled receptor 5; Treg, T regulatory; WR, weight regain; WT, wild type.

and reduces the risk of the development of obesity-related co-morbidities.[3] Consequently, in addition to individuals with a BMI ≥ 40 kg/m^2, bariatric surgery is also considered for individuals with a BMI ≥ 35 kg/m^2 with concomitant metabolic diseases.[4]

While each form of bariatric surgery alters the gastrointestinal tract (GIT) differently, they each reduce an individual's gastric volume to induce varying degrees of weight loss.[5] Sleeve gastrectomy (SG) involves surgically removing 80% of the stomach's curvature and is the most commonly performed procedure due to its relative simplicity, lower complication rates, reduced risk of nutrient and/or drug malabsorption, and comparable outcomes in ameliorating obesity compared with other forms of bariatric surgery.[6–9]

Despite first being performed in 1988, SG's mechanisms of action remain incompletely understood.[10] Initially, SG was primarily considered a restrictive procedure whereby reduced food intake induced substantial weight loss and consequent metabolic, inflammatory, and satiety improvements.[10] However, recent human and rodent studies suggest gastric restriction alone is not responsible for SG-associated benefits. For example, one study reported rodent food intakes returned to pre-surgical levels 2-weeks post-operatively despite displaying sustained weight-loss.[11] This observation suggests gastric restriction alone is not responsible for SG-induced sustained weight-loss, as baseline caloric intake can still be achieved despite a reduced stomach volume.[11] Moreover, altered feeding behavior in rodents and humans, including changes in meal patterning, food reward and macronutrient preference, post-SG cannot be explained by the mechanical effects of stomach reduction alone, but could implicate the involvement of neural inputs along the gut–brain axis.[11–14] Finally, SG-associated metabolic improvements are often observed prior to weight-loss in humans, implying an involvement of weight-independent factors.[15,16]

It is likely the mechanisms behind post-SG benefits are multifactorial, involving a combination of alterations to factors including bile acids (BAs), gastrointestinal hormones, hypothalamic and vagal signaling, and the gut microbiome (GM). Notably, the past two decades have seen a major expansion of scientific publications investigating GM in relation to health and disease.[6]

Therefore, this review will investigate the current literature around the impact of SG on GM composition and function.

2 | SG AND GM COMPOSITION

Animal and human studies report casual links between obesity and dysregulated physiological and biochemical host-GM interactions.[17] Obesity-associated GM dysbiosis is often characterized by reduced GM diversity, loss of commensal bacteria, and pathobiont bloom.

Accumulating evidence suggests GM modification could be implicated in SG-induced weight loss and metabolic, inflammatory, and satiety improvements.[18] Indeed, SG causes GIT anatomical and functional alterations, thus changing food transit times, distal gut pH levels, and feeding behavior, consequently impacting GM architecture and function. While SG-based studies are limited, current literature supports overall favorable GM changes post-SG, including increased diversity and richness, decreased Firmicutes/Bacteroidetes ratio and a shift towards "leaner" microbial phenotypes.[19–21] A recent human study reported five bacterial genera could discriminate between pre and 1-month post-SG, with several bacteria significantly associated with weight-loss (*Bilophila*, *Faecalibacterium*, and *Enterococcus*) and reduced hedonic eating (*Akkermansia*).[13] This suggests SG can induce distinct bacterial GM changes.[13] Likewise, SG-induced pH alterations are reported to favor the presence of Veillonellaceae and Streptococcaceae families, *Akkermansia muciniphila*, *Escherichia coli* and *Bacteroides* spp. and oral microbiome bacteria in humans.[22–24]

Furthermore, several members of the *Bacteroides* genus, including *Bacteroides thetaiotaomicron*, *Bacteroides caccae*, and *Bacteroides ovatus*, are reported to increase in both rodents and humans post-SG.[13,20] Indeed, gavage of *B. thetaiotaomicron* alleviates weight gain and adiposity in high-fat diet (HFD) mice, implying anti-obesity properties.[20] However, *Bacteroides* proliferation could merely represent an adaptation to calorie restriction (CR) post-SG rather than the surgery itself. In fact, *Bacteroides* members, among other mucin-degrading bacteria, can forage host mucus when dietary polysaccharides are scarce, thus conferring them resilience within the human and rodent GM.[25,26]

It is well documented that diet is a major confounding factor due to its influence on GM composition and function, therefore presenting a limitation of the current literature.[27] Interestingly, unlike many other SG-based studies, Paganelli et al. accounted for the impact of routine pre-SG liver shrinking diets (LSDs) on obese GMs of humans with obesity.[22] After 2 weeks of LSD, a sharp decline in alpha diversity was reported, which could reflect GM stress following dramatic changes in patient catabolic states.[22] However, LSD-induced changes, namely, increased Bifidobacteriaceae and decreased Streptococcaceae abundances, were reversed post-SG. These results highlight dynamic changes within the GM throughout the SG timeline and the potential impact of SG-related dietary counseling on GM composition, which may have been omitted in previous studies.

3 | SG AND GM FUNCTION

The GM has coevolved with the human host and is implicated in the normal development and functioning of numerous host physiological processes, including digestion and synthesis of metabolites, strengthening and modulation of the intestinal barrier, neurotransmitter modulation and regulation of immune responses, and the promotion of immune tolerance, as outlined in Table 1.[35] With the observed SG-induced compositional changes within the GM, it is plausible that consequent GM functional changes could contribute towards the SG-associated metabolic, inflammatory, and satiety benefits.

3.1 | Intestinal barrier function and metabolic endotoxemia

The GM plays an important role in the regulation, priming, and maturation of the adaptive and innate immune systems (Figure 1A).

TABLE 1 Summary of interactions between colonic bacteria and human health and disease.

Colonic bacteria	Associations with host health and disease (metabolism, inflammation, and satiety)
Firmicutes/Bacteroidetes	• Increased Firmicutes/Bacteroidetes ratio is generally associated with obesity[28]
Eubacterium and *Ruminococcus* (Firmicutes)	• Encode primary fermentation enzymes and nutrient transporters • Levels increase in obese adults[29,30]
Alistipes, *Parvimonas* and *Fusobacteria*	• Proinflammatory bacteria • Levels increase in obese adults[31]
Bacteroides	• Upregulates gut barrier tight junction protein expression • Reduces LPS translocation[32] • Abundance increases following bariatric surgery[13,20]
Proteobacteria	• Decreases mucus production • Reported risk factor of GM dysbiosis[33]
Lactobacillus plantarum and *Lactobacillus paracasei*	• Anti-inflammatory bacteria • Levels decrease in obese adults[34]
Bifidobacterium	• Reduces LPS levels and improves mucosal barrier function[35,36]
Akkermansia muciniphila	• Modulates gut barrier permeability[37,38] • Levels decrease in obese and T2D adults[37,39,40] • However, increased abundances have been associated with diseases such as multiple sclerosis[41]
Faecalibacterium prausnitzii	• Blocks NF-κB activation, thus inhibiting secretion of proinflammatory mediators[42,43]
Enterococcus	• Associated with reduced hunger levels[13]

Commensal bacteria are critical as active inducers of immune regulatory responses and in establishing immune tolerance to food or other orally ingested antigens.[44] Moreover, the GM indirectly regulates host immune function via intestinal barrier regulation and maintenance. Appropriate intestinal barrier function is integral for preventing excessive translocation of immunostimulatory microbiota and LPS while being selectively permeable for the uptake of essential nutrients and fluids into the circulation.[45]

Indeed, loss of intestinal immune homeostasis is considered an early step preceding the development of systemic low-grade inflammation in obesity.[46] GM dysbiosis, often reported in people with obesity, increases the rate of enteric mucus degradation, thus thinning the intestinal barrier, increasing gut barrier permeability and pathogen translocation.[47] Human participants with obesity subsequently have higher concentrations of plasma LPS, termed metabolic endotoxemia, than lean controls.[45,48] Obese GMs also show increased abundance of LPS-producing bacteria, including *Prevotella* and *Enterobacter* genus, and reduced abundance of beneficial *Bacteroides* and *Bifidobacterium*, which reduce LPS levels and improve mucosal barrier function.[35,36]

While evaluation of the impact of SG on systemic low-grade inflammation and intestinal barrier function remains scarce, the few reported studies provide important novel insights. For example, in obese rats, SG attenuated jejunal expression of proinflammatory cytokines, IL-17, IL-23 and IFN-ϒ.[49] Similarly, SG significantly reduced the inflammatory status of participants with obesity, attributed to decreased serum levels of IL-6, C-reactive protein and thiobarbituric acid and increased serum levels of the anti-inflammatory adipokine, adiponectin.[50] One human study reported an improved inflammatory state 12-months post-SG, which correlated with increased adiponectin and decreased leptin concentrations, increased frequency of mucosal-associated invariant T (MAIT) cells in the colonic mucosa and decreased Th1 cells and regulatory T (Treg) cells in the peripheral blood.[51] Collectively, this data suggests that SG exerts anti-inflammatory effects, which could consequently help to alleviate systemic inflammation and improve metabolic parameters.

Indeed, the GM could contribute to SG-induced anti-inflammatory effects via its role in intestinal barrier maintenance and immune regulatory metabolite production. However, there are very few reported studies investigating the GM and host immune system interactions post-SG. Nevertheless, two studies recently investigated gastrointestinal permeability post-SG, which could indirectly reflect GM-immune system interactions and intestinal barrier regulatory changes. Wilbrink et al. and Kellerer et al. reported decreased gastroduodenal and small intestinal permeability post-SG, which could help to reduce pathogen and LPS translocation and consequent systemic inflammation and metabolic endotoxemia in subjes with obesity.[19,52] This hypothesis correlates with a previous study that reported reduced bacterial DNA translocation post-SG in subjects with obesity.[53] However, unexpectedly, Kellerer also reported no overall decrease in paracellular permeability and continued LPS translocation due to increases in colonic permeability post-SG.[19] This further highlights the complexity of intestinal barrier homeostasis and warrants future larger scale investigations into SG-induced permeability changes along the length of the GIT. Additionally, the same group previously revealed that following a 4-week very low-calorie diet, intestinal barrier integrity improved and was associated with reduced systemic inflammation in women with obesity.[54] Therefore, dietary changes post-SG could also contribute to alterations in gastrointestinal permeability rather than solely post-surgical effects.

3.2 | Energy metabolism

Increasingly, studies report the essential role of GM for dietary energy harvest, storage, and expenditure and the related regulation of the host metabolic state (Figure 1B). For example, the GM enables energy extraction from otherwise indigestible macronutrients by providing a variety of metabolic enzymes not expressed by the human host.[25,55] The GM also produces short-chain fatty acids (SCFAs), which

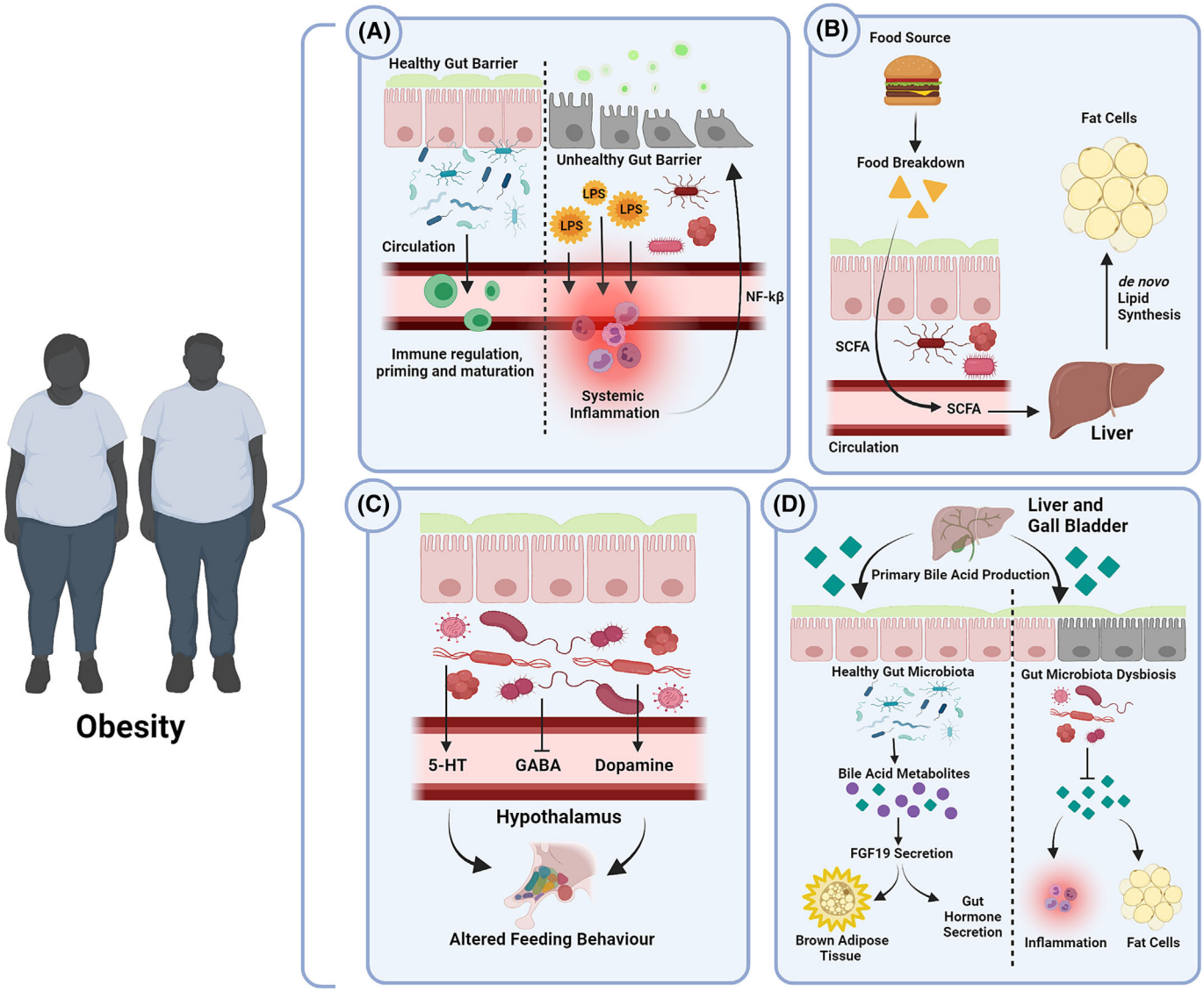

FIGURE 1 Proposed mechanisms through which the gut microbiome affects host obesity: (A) gut barrier health, (B) energy metabolism, (C) feeding behavior, and (D) bile acid metabolism. Created with BioRender.com.

influence neuroendocrine pathways that form the gut–brain axis and are implicated in the regulation of host satiety and energy metabolism.[56,57]

Fecal microbial transplant (FMT) studies report that colonization of germ-free (GF) mice with obese GM results in significantly greater increases in total body fat than colonization with lean GMs.[29] Similarly, a human study reported that overfeeding correlated with higher stool energy loss in lean participants compared with participants with obesity.[58] GM functional shifts, promoting increased dietary energy harvest and adiposity, are thought to be attributed to enrichment of genes encoding energy harvesting enzymes in obese GMs. For example, one study reported an enrichment of *Eubacterium rectale* genes that encode for primary fermentation enzymes that digest dietary polysaccharides, ABC nutrient transporters, and α- and β-galactosidases that generate SCFAs, acetate, and butyrate, in participants with obesity.[59,60]

Metagenomic and metabolomic studies have helped to provide key links between GM changes and metabolic improvements post-SG. For example, Shao et al. reported SG-induced metabolic improvements associated with increased duodenal *Lactobacillus* spp. richness and increased hypoxia-inducible factor 2α (HIF-2α) signaling in HFD-mice.[61] Interestingly, chronic administration of *Lactobacillus* spp. probiotics to HFD-mice reduced weight gain, improved glucose tolerance, and upregulated HIF-2α signaling.[61] This highlights the possible role of GM alterations in SG-induced metabolic benefits.

In humans with obesity, Damms-Machado et al. reported SG-induced shifts towards leaner GM phenotypes, attributed to a reduced Firmicutes/Bacteroidetes ratio.[21] Additionally, GM energy reabsorbing potential decreased post-SG, noted by increased loss of energy rich fecal substrates, suggesting that SG-induces GM functional shifts favoring reduced energy harvest, potentially attributed to decreased Firmicutes abundance.[21] However, similar Firmicutes

reductions have been reported in CR weight-loss interventions, therefore suggesting that SG-associated GM changes may not solely be because of the surgery itself.[62] Furthermore, there are reported Firmicutes/Bacteroidetes ratio discrepancies in SG-based investigations, with some studies reporting increased or no Firmicutes/Bacteroidetes ratio changes post-SG.[63,64] Despite these findings, the Firmicutes/Bacteroidetes ratio does not provide sufficient details of host GM composition and functional changes. Indeed, species of the same phyla and across species may differ functionally and in abundance dependent on host disease state.[65] Therefore, studies using the Firmicutes/Bacteroidetes ratio may overlook important GM changes and should alternatively use more detailed analysis approaches, including whole genome shotgun sequencing, to confirm these results. Shotgun sequencing, unlike the commonly used 16S ribosomal RNA gene sequencing, relies on metagenomic databases to sequence and assign bacterial DNA from whole communities to specific taxa and profile metabolic functions, therefore providing a deeper characterization of the GM complexity.

Liu et al. utilized shotgun sequencing and reported SG-induced GM functional shifts in pathways involved in carbohydrate fermentation, citrate cycle, glycosaminoglycan degradation, lipopolysaccharide (LPS) synthesis, amino acid biosynthesis, and glutamate transport.[20] Similarly, Murphy et al. used shotgun sequencing and reported distinct changes in the GM's energy utilization capacity between baseline and 1-year post-SG.[66] Diabetes remission post-SG was also associated with increased *Roseburia intestinalis* abundance, a bacterium that has previously been associated with improved insulin sensitivity.[66,67] Collectively, these studies suggest that SG induces positive GM-related metabolic changes.

3.3 | Feeding behavior

Obesity is further characterized by perturbations in hedonic feeding behaviors involving food motivation (Figure 1C).[68] The GM modulates and produces several neurotransmitters, including dopamine, 5-hydroxytryptamine (5-HT), and gamma-aminobutyric acid (GABA), which regulate feeding behavior.[69]

Numerous studies have reported reduced appetite and altered food preference post-SG, suggesting gut–brain axis involvement.[12,70] Sanmiguel et al. are one of the few to investigate GM and post-SG feeding behavior alterations.[13] In human subjects with obesity, fasting hunger levels significantly and rapidly decrease post-SG and strongly correlate with *Enterococcus* abundance.[13] However, the study did not provide proof of causality between *Enterococcus* abundance and feeding behavior. Moreover, previous studies have reported *Enterococcus* bloom following fiber supplementation in HFD-obese rats, which was similarly associated with reduced fat deposition and satiety.[71,72] Therefore, *Enterococcus* proliferation could be attributed to dietary changes post-SG, namely, reduced calorie intake (and possibly improved fiber intake), rather than surgery alone.

Lastly, Sanmiguel reported weak correlations between *Akkermansia* abundance and reduced appetite, hedonic eating ratings, and sweet preference post-SG.[13] This is consistent with previous studies whereby *A. muciniphila* was reported to increase activation within the endocannabinoid system, consequently stimulating glucagon-like peptide (GLP)-1 secretion and promoting an anorexigenic incretin profile.[39] The GM has also been reported to regulate expression and function of gut heterodimeric proteins (sweet receptors), with GF mice displaying an exaggerated preference for sucrose-rich foods.[73] Overall, while Sanmiguel's study provides novel insights into the interactions between the GM and feeding behavior post-SG, the small sample size has been acknowledged as a limitation for this study, along with a lack of control for dietary cofounders.[13] Therefore, the mechanisms that underlie changes in SG-associated hedonic eating and food preference alterations remain unclear.

Studies have also reported distinct GM nutrient metabolism shifts post-SG, including amino acid biosynthesis and transport (particularly glutamate), which indirectly influences feeding behavior.[20,66] Glutamate, a dominant excitatory neurotransmitter, stimulates appetite and, in high concentrations, is associated with obesity.[74] Liu et al. reported that subjects with obesity exhibited high serum glutamate levels, which inversely correlated with the abundance of glutamate-fermenting commensal *B. thetaiotaomicron*.[20] These obesity characteristics were partially reversed post-SG, as demonstrated by decreased glutamate levels, decreased abundance of *Ruminococcus* (implicated in glutamate biosynthesis), and increased *B. thetaiotaomicron* abundance (implicated in glutamate fermentation).[20] Consistently, previous human and rodent studies report *B. thetaiotaomicron* colonization increased levels of mRNAs encoding glutamate transporter and glutamate decarboxylase in epithelial cells, which correlated with improved insulin sensitivity and inflammatory state.[75,76] Together, these studies suggest SG-associated GM changes could influence neurotransmitter production and indirectly alter host feeding behavior and metabolic state.

3.4 | BA metabolism

BA and GM interactions have increasingly been linked with host metabolism regulation, with their dysregulation associated with metabolic disease. Primary BAs, namely, chenodeoxycholic acid and cholic acid, can be conjugated with glycine and taurine to form bile salts for lipid digestion and absorption. Although up to 95% of these BAs actively enter the enterohepatic circulation, the remaining BAs are further modified by the GM to form secondary BAs via deconjugation and dihydroxylation.[77] Secondary BA production induces the activation of the Farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR-5), which are essential for glucose tolerance and insulin sensitivity within the liver and intestine.[57]

Human subjects with obesity are frequently reported to exhibit increased fasting serum BA levels, which are attributed to augmented and dysregulated BA synthesis and decreased BA pool diversity.[78,79] Obesity-associated GM perturbations strongly influence GM-dependent BA metabolic pathways, consequently disrupting host metabolic processes including insulin sensitivity and lipid and

carbohydrate metabolism (Figure 1D). Primary and secondary BA pool alterations may also contribute to obesity-associated low-grade intestinal inflammation and increased intestinal permeability.[77,80,81]

SG increases circulating serum BA levels and levels of conjugated and unconjugated BAs, independent of energy restriction, in subjects with obesity and in HFD-induced obese mice.[82,83] Indeed, SG impacts BA enterohepatic circulation levels and composition both directly via upper GIT alterations and indirectly via SG-induced GM alterations. The close bidirectional relationship between the GM and BAs is facilitated via FXR and TGR-5 signaling and is hypothesized to contribute to SG-induced metabolic improvements. Pioneering work by Ryan et al. showed that while SG altered the relative abundances of *Bacteroides* and *Roseburia* in wild-type (WT) mice, these changes were not observed in FXR knock out (KO) mice.[84] Moreover, FXR KO mice failed to exhibit weight loss or improved glucose tolerance following SG, thus implicating a potentially important role for BA–GM FXR signaling in the metabolic benefits of SG. However, it remains unclear which specific GM changes correlate with altered FXR signaling post-SG.

Another study demonstrated that glucoregulation improvements and favorable shifts in BA pool profiles post-SG were attenuated in TGR-5 KO mice relative to WT mice.[85] However, bacterial species known to play an important role in BA metabolism did not differ between WT and TGR-5 KO mice, suggesting that TGR-5-mediated GM population alterations did not contribute to SG-induced BA profile shifts.[85]

However, another study reported a GM-induced increase in gut expression of BA transporters *Asbt* and *Ostα* post-SG in mice.[86] This increased transport of microbial-derived BA lithocholic acid (LCA) and consequent activation of the gut–liver pathway led to increased synthesis of cholic acid-7-sulfate (CA7S), a TGR-5 agonist, thus improving mouse hyperglycemic state.[86] Moreover, inhibition of these BA transporters within the portal vein has previously been shown to impair glucose tolerance, insulin sensitivity, and GLP-1 secretion in mice.[87] Therefore, SG-induced alterations in GM-derived BA exchange across the enterohepatic axis could contribute to the metabolic benefits observed post-SG.

However, further metagenomic and metatranscriptomic analysis is needed to determine whether there are shifts in overall GM enzyme gene expression post-SG that could influence BA-FXR and TGR-5 signaling pathways and consequent metabolic parameters.

4 | WEIGHT REGAIN (WR) FOLLOWING SG

Similarly to outcomes from other types of bariatric surgery, SG is associated with long-term WR. Abnormal WR is defined as the progressive WR that occurs following achievement of an initial successful weight loss, classified as an excess weight loss percentage (EWL%) > 50%.[88] Following SG, abnormal WR has been reported to range from 14% to 37% at ≥7 years post-operatively.[89] Additionally, weight-loss outcomes present large inter-individual variability, with some patients deemed good responders (i.e., losing sustained and large amounts of weight) while others lose less or regain weight post-operatively. While clinical and biological factors, namely, conversion from laparoscopic to open surgery or adipose tissue fibrosis, may contribute to weight-loss variability, recent studies suggest an involvement of differential GM changes.[90,91] While SG induces significant GM compositional changes, it may not rescue obesity-associated GM dysbiosis.[20,91] Partial GM recovery or GM adaption to pre-surgical levels could contribute to abnormal WR or the reoccurrence of obesity-associated comorbidities, thus calling for additional strategies to improve GM composition and function.

Interestingly, Shen et al. reported that while GM diversity and composition changed rapidly at 3-months post-SG, alterations regressed to pre-surgical levels by 12 months in humans with obesity.[64] GM reversal towards pre-surgical characteristics could predict future whole-body metabolic deteriorations and potentially the need for additional therapeutic strategies to maintain beneficial GM changes. Interestingly, Thaiss et al. identified GM signatures that persisted after successful dieting in obese mice and contributed to faster WR and metabolic aberrations upon re-exposure to obesity-promoting conditions.[92] Furthermore, this accelerated WR phenotype could be transmitted to GF mice through FMT. Therefore, identification of common GM signatures post-SG could help to explain why some individuals are more receptive to SG-induced weight-loss and metabolic benefits than others.[93] Furthermore, the identification of metabolically favorable GM signatures could lead to the development of GM targeting strategies aimed at improving metabolic, inflammatory, and satiety outcomes following SG and reducing future post-operative WR. However, the benefits of probiotic administration to improve health via changes in GM signatures remain debated.[94]

Furthermore, WR phenotypes post-SG could also stem from poor adherence to post-operative dietary advice, justifying further investigation into the underlying mechanisms of this phenotype.

5 | LIMITATIONS AND FUTURE PERSPECTIVES

The variability of data from reported studies is evident throughout this literature review. While some studies report considerable GM compositional and functional shifts,[66] other GMs remain relatively stable post-SG.[22] Moreover, there appears to be no defined obese-GM composition or function, as demonstrated by large study inter-variability. This poses the question, which GM composition or function is most representative of an obese state or post-SG? While the discussed literature provides key insights into the role of the GM in obesity and SG-induced outcomes, it is essential to consider the inherent limitations of existing studies, which may have contributed to the study's inter-variability of data.

5.1 | Rodent versus human studies

In the first instance, it is important to note the relative novelty of this field of research. Consequently, most GM data derives from rodent-

based studies. However, it remains debated whether rodent study findings can be translated to humans due to several unique factors that influence rodent GMs, including the impact of the cage, vendor, and facility.[95] Additionally, rodents recover some of their energy requirements from copraphagia, which influences the colonic microbiome in a manner that does not apply to humans. Furthermore, rodents are highly inbred strains and do not display human diversity. Therefore, characteristic rodent traits are likely to be diluted in a human setting. Lastly, rodents and humans present significant differences in the timings and changes in body weight and food intake following SG.[14] For example, rodents predominantly lose fat rather than lean mass post-SG, whereas humans lose both lean and fat mass.[11,96] Moreover, rodent body mass and food intake nadir is around 2–3 weeks yet 6–18 months in humans, dependent on percentage total weight loss.[14,97] This makes extrapolating rodent-based data to humans in SG studies more challenging. However, despite the limitations of animal models, they remain vital for understanding the biological impact of SG and the mechanisms underlying its benefits. Overall, inferring rodent-based data to human data should be done with caution.

5.2 | Observational versus interventional studies

Next, while there has been a significant expansion of human-based GM studies, investigations remain in their infancy. For this reason, most human studies are observational in nature; therefore, data are based on association rather than causation, thus reducing data interpretation and reproducibility. Consequently, it remains unclear whether the GM is implicated in obesity development and SG-associated benefits or whether reported GM alterations are merely an epiphenomenon due to changing environmental conditions. To prove causality, intervention studies, namely, FMT, are required to manipulate colonic microbiomes while being able to observe subsequent changes in metabolic, inflammatory, and satiety markers. Intervention studies could be key to developing GM targeting strategies for obesity prevention and improving SG efficacy. However, while FMT has long been a therapeutic treatment for recurrent *Clostridium difficile* infection, FMT can lead to unintended consequences such as WR.[98] Additionally, a lack of safety data on long-term FMT risks presents a major barrier in human intervention studies. Overall, there is a clear need for proof of causality in human GM-based studies to improve data reproducibility and further understanding of the involvement of GM in obesity and SG-associated outcomes.

5.3 | Sample size

Small sample sizes present another drawback to current human GM-based studies. Indeed, smaller sample sizes mean that studies are often unable to control for cofounders, which can affect the reliability and consistency of GM composition and function data. Importantly, GM composition is influenced by a myriad of factors, including, but not limited to, study design variations, geographic location, gender, age, baseline GM compositions, gastrointestinal comorbidities, medication history, and diet. Each variable deserves special attention as each has the potential to significantly alter the GM, consequently influencing outcome data and contributing to study inter-variability. For example, diet is a major driving factor for rapid GM diversity and functional alterations and remarkably accounts for up to 57% of GM inter-individual variation, compared with just 12% by human genetic variation.[99] Moreover, dietary changes are reported to alter GM composition within days, highlighting the dominant dietary influence on shaping the GM.[100] However, despite this, most studies fail to account for the multiple dietary changes patients typically undertake during the SG timeline, which could potentially induce important biases on GM evaluations.[22] Future studies should aim to evaluate the GM: (i) before patients are introduced to LSDs, (ii) 2 weeks post LSD, (iii) 2 weeks after post-SG liquid diet, and (iv) after the liquid diet has ceased and regular food can be consumed. Accounting for each dietary change along the SG pathway reduces the potential for dietary counseling bias.

5.4 | Antibiotics

In addition, SG patients routinely receive peri-antibiotics to provide surgical site infection prophylaxis and reduce rates of post-surgical wound infections.[101] Animal models suggest short term antibiotic administration disrupts GM structure, increases adiposity, and diminishes weight-loss and metabolic benefits post-SG.[102,103] Interestingly, one study identified persistent GM composition alterations 1 month after the last dose of antibiotic, highlighting a longitudinal impact.[103] However, the impact of a single dose of intestinal penetrating antibiotic post-SG has gone largely undocumented but could have long-lasting effects for months or even years.[104–107] Nalluri et al. reported that the immediate post-operative GM shift post-SG is significantly impacted by a single dose of antibiotic administration, more so than CR or resultant anatomical changes.[101] Future studies should consider the necessity of peri-operative antibiotics and the type of antibiotics used post-SG. Overall, characterizing the impact of important cofounders, namely, dietary counseling and antibiotic use, on the GM is vital for understanding the consequences of these interventions and for maximizing SG efficiency.[101]

5.5 | Study length

Next, possibly because of small sample sizes, current SG-based studies only report GM compositional and functional shifts in the short and mid-term. It remains unclear whether reported post-SG GM signatures are sustained or whether they are merely short or mid-term adaptations to gastrointestinal alterations, such as altered pH, increased oxygen content, and BA delivery.[22,66] Longitudinal studies, greater than 1-year post-SG, could help to determine whether GM signatures are sustained and enable novel insights into the molecular mechanisms involved in sustained weight-loss and metabolic, inflammatory, and satiety improvements post-SG. The sustainability of GM signatures could help to reveal why some individuals are more receptive to SG than others and suggest

the potential administration of additional therapeutic strategies for the maintenance of beneficial GM changes. Alternatively, findings of unsustained GM changes suggest GM-independent mechanisms are implicated in SG-associated metabolic outcomes, therefore warranting further investigation.

However, while small sample-size studies present their limitations, it is also important to consider the benefits of investigating individual variability in small sample-sized studies. Larger-scale studies may hide the unique and complex interplay of genetic and environmental factors that mold an individual's GM composition, obesity presentation, and SG-associated outcomes. Therefore, there is also a need for more studies focusing on single individuals, known as *N*-of-1 trials, particularly for the development of personalized GM-targeting therapies.[108]

5.6 | GM analysis methods

Next, differences in GM analysis methods and techniques make study comparisons challenging and could account for varied GM compositional and functional changes across obesity and SG-based studies. Utilizing 16S rRNA sequencing has long been the gold standard for bacterial phylogenetic analysis due to its affordability, robustness, and ease of performance. However, 16S rRNA sequencing has several limitations, including an inability to provide sufficient resolution for the differentiation of species and strains with high homology across the 16S gene. This generates under/over representations of specific taxa, thus limiting the scope of quantitative analysis. Moreover, variable region choices for 16S rRNA sequencing can cause inter-study variability. For these reasons, whole genome shotgun sequencing is arguably superior to 16S rRNA sequencing and provides deeper GM characterization due to its higher resolution and species identification accuracy.[109] However, the higher cost of shotgun sequencing compared with 16S rRNA sequencing, due to higher coverage (10–30 million reads) and more complex downstream data analysis, is challenging in many applications. Therefore, a standardized GM analysis method should be developed to help improve data reproducibility and aid future study comparisons in both obesity and SG-based studies.

Another limitation of GM analysis in current obesity and SG-based studies is that they often only consider GM DNA, thus failing to

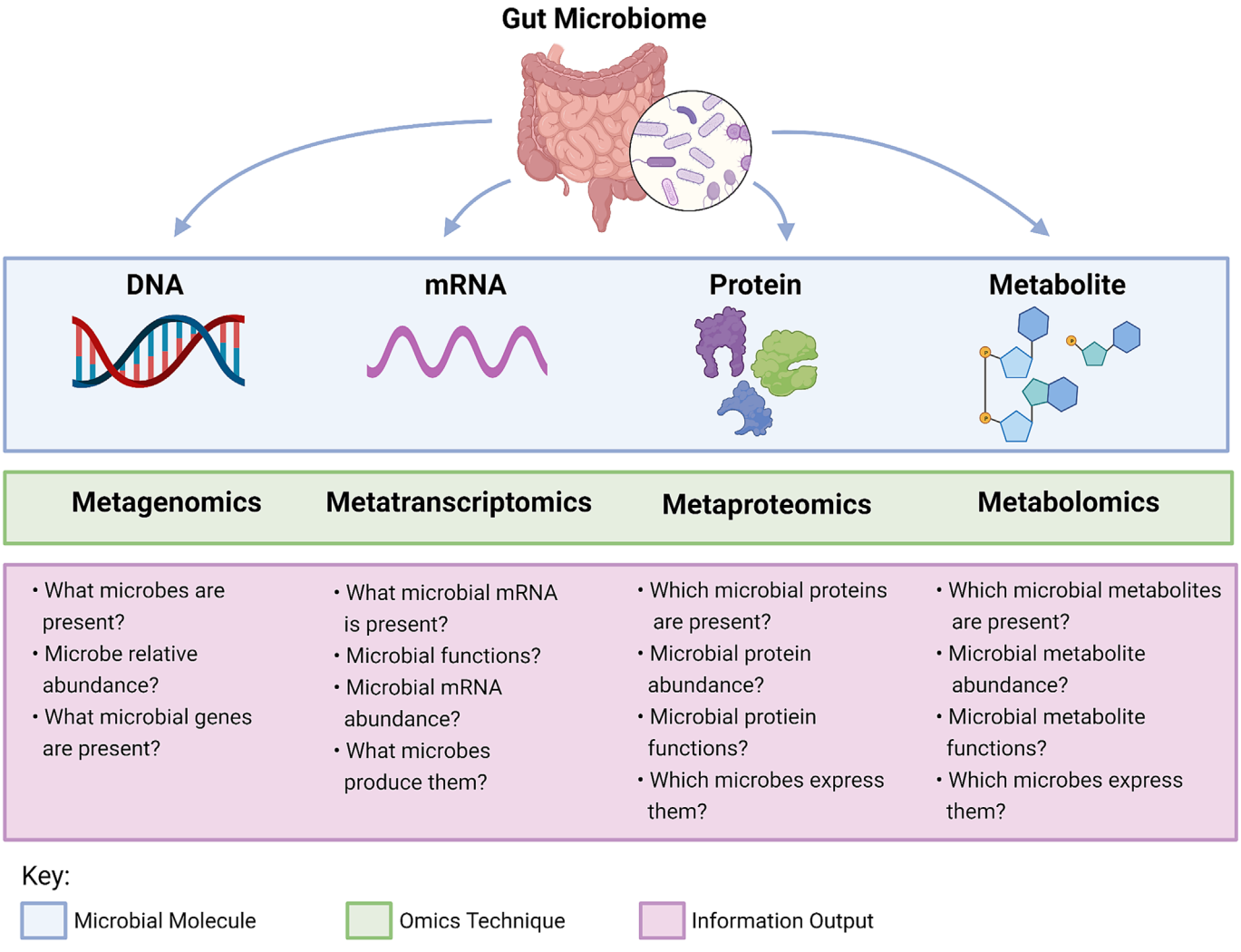

FIGURE 2 Multi-omics approaches for gut microbiome analysis. Created with BioRender.com.

study both active and dormant bacterial forms. For this reason, multi-omic approaches including metagenomics, metatranscriptomics, metaproteomics, and metabolomics are increasingly being used collectively to gain a more holistic picture of the GM community, structure, and functional status (see Figure 2).[110] While each omic branch has its limitations, combining different omic techniques increases the accuracy and reliability of the data and is essential for understanding the holistic effect of SG on the GM and establishing correlations with metabolic, inflammatory, and satiety benefits and host physiology.[111]

Furthermore, studies often only consider the scolonic microbiome due to its accessibility through fecal sampling. However, it is worth noting that the GM extends throughout the entire GIT. It is therefore possible that important GM changes occur more proximally within the GIT and could play important roles in regulating host metabolic, inflammatory, and satiety pathways post-SG and in obesity. Indeed, SG decreases gastric acid contents, thus increasing the jejunum pH, which may influence the GM more proximally than in the colon.[112] More comprehensive GM data could be obtained through endoscopy by using tools such as biopsy forceps and luminal brushes. However, endoscopy is invasive, and samples can be contaminated by endoscopic channel contents.[113] Alternatively, ingestible devices have gained significant interest due to their ability to collect intestinal samples with minimal patient discomfort. However, like endoscopic methods, samples collected from ingestible devices are easily contaminated. Developing more accurate sampling methods is critical for future GM research and should aim to achieve GM analysis along the entire GIT.

5.7 | Gut mycobiota

Lastly, most obesity and SG-based GM studies only investigate GM bacteria composition and function. While bacteria represent the most abundant component of the human GM, fungi represent a greater biomass.[114] Although the field investigating gut fungi communities (termed gut mycobiota) remains in its infancy, studies have reported differences between human subjects with obesity and lean individuals.[115] It would be interesting to investigate the symbiosis between gut bacteria and fungi in the context of obesity and post-SG.[116]

6 | CONCLUSIONS

To conclude, despite the infancy of research, current literature supports an important role of the GM in metabolic and inflammatory dysregulation and alterations of feeding behavior observed in obesity. Undoubtedly, subjects with obesity have significantly different GMs compared with lean controls. Moreover, GM changes post-SG provide compelling evidence for the beneficial role of specific GM bacterial species on host health and wellbeing. Current literature suggests that the GM contributes to the development of obesity and SG-associated outcomes via several mechanisms involving energy harvest, gut barrier permeability, gut–brain axis signaling, and BA metabolism.

Given the vast variation and limitations within the literature on GM, obesity, and SG-based studies, further focused research is still required. It remains unclear whether the GM contributes to obesity development and SG-associated metabolic, inflammatory, and satiety outcomes or whether these changes are merely epiphenomena from altered environmental conditions. Indeed, most human studies to date are based on associations rather than causations, thus limiting their interpretation and reproducibility. Moreover, small sample sizes limit the ability of SG-based studies to remove key confounding factors, which could significantly affect GM signatures, thus skewing data interpretation. Lastly, GM analysis is inconsistent among obesity- and SG-based studies, making study comparisons problematic. Future studies investigating the association of the GM with obesity and SG outcomes should address current study limitations and move beyond associative data to generate firm-evidence-based research. Ultimately, the GM represents an indispensable tool to improve the efficacy of current weight-loss strategies and for the development of novel obesity treatments aimed at targeting the GM.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest statement.

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