nature reviews microbiology

https://doi.org/10.1038/s41579-023-00888-0

Review article

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Roles of the gut microbiome in weight management

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Abstract

Overweight, obesity, undernutrition and their respective sequelae have devastating tolls on personal and public health worldwide. Traditional approaches for treating these conditions with diet, exercise, drugs and/or surgery have shown varying degrees of success, creating an urgent need for new solutions with long-term efficacy. Owing to transformative advances in sequencing, bioinformatics and gnotobiotic experimentation, we now understand that the gut microbiome profoundly impacts energy balance through diverse mechanisms affecting both sides of the energy balance equation. Our growing knowledge of microbial contributions to energy metabolism highlights new opportunities for weight management, including the microbiome-aware improvement of existing tools and novel microbiome-targeted therapies. In this Review, we synthesize current knowledge concerning the bidirectional influences between the gut microbiome and existing weight management strategies, including behaviour-based and clinical approaches, and incorporate a subject-level meta-analysis contrasting the effects of weight management strategies on microbiota composition. We consider how emerging understanding of the gut microbiome alters our prospects for weight management and the challenges that must be overcome for microbiome-focused solutions to achieve success.

Sections

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Introduction

Chronic energy imbalances impact one-third of the global human population. By recent WHO estimates[1,2], 1.9 billion adults and 380 million children worldwide are either overweight or obese, with obesity rates tripling since 1975. An additional 462 million adults and 200 million children are undernourished, with undernutrition contributing to 45% of deaths among children under 5 years of age. Individuals in developing countries and with low-socioeconomic status face disproportionately large burdens of undernutrition plus some of the fastest rising rates of overweight and obesity[3]. Related morbidities can simultaneously reduce productivity and increase medical expenses, reinforcing links between poverty and poor health. The consequences of energy imbalance are therefore profound and long lasting for personal and public health, economic development and social justice.

One reason for the large and growing scale of this problem is that existing treatments have displayed limited long-term success. Overweight and obesity are typically treated with lifestyle interventions that induce a negative energy balance by lowering caloric intake and increasing physical activity, with obesity also treated pharmacologically and/or surgically. Such interventions often succeed in the short term, with most people who are overweight able to lose >5% of initial weight over a 6-month period[4]. However, there is almost invariably weight regain as acute negative energy balance triggers metabolic adaptations favouring resource sparing and a lower resting metabolic rate[5,6]. Undernutrition is typically treated with ready-to-use therapeutic foods that aim to increase calorie and/or protein intake, antibiotics to combat co-infections and structural changes ameliorating food security. However, these interventions often prove insufficient to rectify undernutrition, particularly in young children. Compounding the problem, undernutrition in early life can alter development that then predisposes individuals to metabolic comorbidities as adults[7], with some effects even transmissible to subsequent generations[8].

There remains a pressing need for new approaches to weight management. Recent transformative research has illuminated profound and widespread influences of the gut microbiome on human physiology, including energy balance. The gut microbiome has proven sensitive to existing tools for weight management, including diet and exercise, drugs and surgical interventions such as gastric bypass. Critically, variations in the gut microbiome can also modulate the efficacy of interventions, suggesting that rational manipulation of the gut microbiome could facilitate weight management. Here, we outline the roles of the gut microbiome in energy metabolism, review bidirectional influences between the gut microbiome and existing tools for weight management and evaluate opportunities and challenges in the development of microbiome-directed therapies targeting energy balance (Fig. 1). Although most research to date has focused on gut microbial contributions to overweight and obesity, where possible, we draw attention to parallel advances towards elucidating and manipulating the role of the gut microbiome in undernutrition, a promising new frontier for microbiome-targeted medicine.

Gut microbiome and energy metabolism

Germ-free mice reared in sterile conditions have lower adiposity compared with conventionally raised mice or formerly germ-free mice colonized with murine or human gut microbiota[9,10], despite germ-free animals eating more and expending less energy[9]. Similar results have been observed in mice harbouring antibiotic-ablated gut microbiotas[11]. Such studies have illustrated a strong, generally net-positive effect of microbial colonization on host energy status. Moreover, numerous studies have shown that metabolic phenotypes such as obesity, insulin resistance, low-grade inflammation and/or elevated thermogenesis can be recapitulated in gnotobiotic animals through microbiota transplantation, suggesting causal impacts of the gut microbiome in energy metabolism[12,13]. Germ-free animals display physiological and immunological abnormalities compared with conventional mice[14,15], including in phenotypes relevant to energy balance such as gut barrier function[16], expression of enzymes involved in nutrient acquisition and utilization[17] and gross physiology of the absorptive surface[18]. Human-to-mouse microbiota transplants also do not perfectly replicate human donor composition[19], and the resource-intensive nature of gnotobiotic animals often leads to underpowered experiments[20]. Despite these limitations, gnotobiotic animal models remain among our best tools for establishing cause and effect between microbiome composition and host energy balance.

Gnotobiotic studies have enabled us to establish that the gut microbiome causally modulates both sides of the energy balance equation. For instance, the gut microbiome regulates host energy intake via short-chain fatty acid (SCFA)-mediated hormone secretion as well as direct microbial synthesis of neurotransmitters and hormone mimics that interact with the enteric and central nervous systems to regulate hunger and satiety (Box 1). The gut microbiome

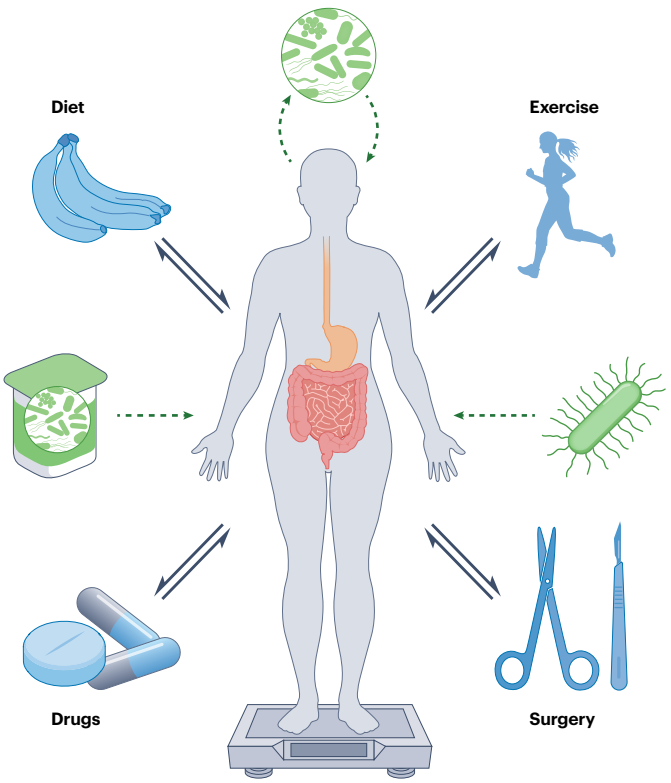

Fig. 1 | Reciprocal influences between the gut microbiome and key lifestyle and clinical approaches for weight management. Common weight-modulating interventions (blue) such as diet, exercise, drugs and surgery impact gut microbial structure and function, and these changes in the gut microbiome in turn alter intervention efficacy. Gut microbial contributions to weight management are targeted by emerging microbiome-directed therapies (green), including foods engineered to support the engraftment or growth of beneficial microorganisms, autologous faecal microbiota transplantation after weight loss and next-generation probiotics.

increases dietary energy harvest by enhancing small intestinal lipid absorption and salvaging energy from carbohydrates and proteins escaping digestion in the small intestine via fermentation to SCFAs and other metabolites with residual caloric value (Fig. 2). The gut microbiome directs energy utilization by generating metabolic substrates accessible to select host tissues, regulating bile acid metabolism and influencing the expression of host genes controlling fatty acid uptake, lipolysis and thermogenesis (Fig. 3). Finally, the gut microbiome affects interactions between energy balance and inflammation by training systemic immunoreactivity during development, influencing gut barrier integrity and generating pro-inflammatory products such as lipopolysaccharide and flagellin with variable consequences for metabolic health (Box 2). As many of these observations derive from animal research, future studies in humans will be needed to establish translational relevance.

Whether manipulation of energy status by the gut microbiome is beneficial or detrimental depends, of course, on context. Studies at the positive and negative extremes of energetic balance have generally reported that the gut microbiome exacerbates host energetic phenotypes. For instance, the gut microbiome associated with hosts who are obese harbours structural and functional changes that increase the capacity for dietary energy harvest[21]. Similar weight-potentiating results have been found in dynamic states of positive energy balance, including weight rebound after caloric restriction[22], relapsing obesity on reintroduction of obesogenic conditions after weight cycling[23] and among women in the third trimester of pregnancy[24]. The gut microbiome can also exacerbate acute states of negative energy balance. For instance, the gut microbiome of children with kwashiorkor, a form of severe acute malnutrition, exhibits a juvenilized state that impairs nutrient uptake[25,26]. Likewise, the gut microbiome following Roux-en-Y gastric bypass (RYGB) surgery, a period when weight is shed quickly, has been shown to causally contribute to weight loss[27]. Similarly, gnotobiotic recipients of microbiomes conditioned on very-low-calorie diets (~800 kcal per day) had decreased adiposity versus recipients of pre-diet microbiomes[28]. Critically, gnotobiotic transplant recipients of kwashiorkor-associated and post-RYGB-associated microbiotas exhibited lower body mass and adiposity versus germ-free mice[25,27], providing rare examples of microbiomes with net-negative influences on host energy status.

However, the gut microbiome does not always act to exacerbate energy imbalance. Indeed, under at least some conditions, the host–microbial system exhibits a form of dynamic energetic buffering in which short-term reductions in energy uptake by the host foster a microbiome with potentiated contributions to energy status. For instance, in mice fed nutrient-matched raw and cooked diets known to differ in ileal digestibility, the lower digestibility raw diet led to weight loss overall but fostered a gut microbiome that itself promoted increased host energy status, as evidenced by greater weight and adiposity gains among gnotobiotic recipients of microbiotas conditioned on raw diets[29]. The specific conditions under which the gut microbiome exacerbates versus buffers host energy status remain unclear, but constitute a high-priority area for research because such conditions reveal levers for therapeutic manipulation of the gut microbiome.

Another challenge in connecting microbial signatures to metabolic phenotypes is that there could be present consequences of past microbiome states. Studies in mice and humans suggest that disruption of the gut microbiome in early life through pulsed therapeutic or chronic subtherapeutic doses of antibiotics confers increased risks of adult adiposity[11]. Metabolic consequences of disrupted early-life gut microbiomes were found even when microbiome signatures ultimately rebounded to become indistinguishable from controls[30], suggesting that some metabolic contributions of the microbiome will be challenging to track. The proximate mechanisms linking disrupted early-life microbiomes with adult host energetic phenotypes await elucidation. For instance, it remains unknown whether the excess energy that predisposes to obesity comes from increased food

Box 1

Influences of the gut microbiome on energy intake

Microbial metabolites can alter feeding behaviour, as exemplified by the exogenous delivery of short-chain fatty acids (SCFAs) reducing appetite[173,174]. These effects are thought to be mediated through the gut–brain axis, a signalling network linking the central and enteric nervous systems. Within the gut, SCFAs activate GPR41 and GPR43 receptors on enteroendocrine L-cells, triggering the release of glucagon-like peptide 1 and peptide YY[175,176]. These hormones promote satiety by activating endocrine receptors in the hypothalamus and nucleus of the solitary tract, which process information about nutritional status. SCFAs may also affect energy intake by signalling through the vagus nerve[174] or, in the case of acetate, by crossing the blood–brain barrier and inducing the expression of anorexia-promoting genes[177]. Many gut bacteria synthesize peptide mimics of hormones regulating satiety and hunger, such as leptin and insulin[178]. Gut microorganisms can also synthesize neurotransmitters such as GABA, dopamine, acetylcholine and noradrenaline[179], as well as affect endogenous levels of serotonin in the intestine[180] and dopamine, noradrenaline and serotonin in the brain[181]. These neurotransmitters can affect energy intake through their roles in gut motility, satiation and food reward.

Whether the gut microbiome impacts food preferences in humans remains unknown, but such evidence is emerging among animal models. Compared with conventional mice, germ-free mice have higher expression of intestinal receptors for sweet taste and increased sucrose intake[182], as well as increased preference for fat, a result coupled to increased expression of oral fatty acid receptors and decreased expression of satiety peptides[183]. Faecal microbiota transplants from diet-induced obese mice into germ-free recipient animals were sufficient to transfer the blunted preference for high-fat high-sugar diets observed among the donors and were associated with lower markers of food reward[184]. Most strikingly, colonization of germ-free mice with gut microbiota from herbivorous, omnivorous or carnivorous wild rodents affected macronutrient intake, with recipients of a herbivorous microbiome selecting diets with higher protein versus carbohydrate[185], potentially because protein is limiting on a plant-based diet. The colonic microbiota of herbivores is also nitrogen limited, raising the possibility that microorganisms manipulate host-feeding behaviour for their own benefit[186]. Conversely, fruitflies fed an essential amino acid-deficient diet prefer foods containing microbial taxa capable of ameliorating the deficiency, raising the possibility that hosts also harbour some capacity to select for beneficial microbial functions via diet[187].

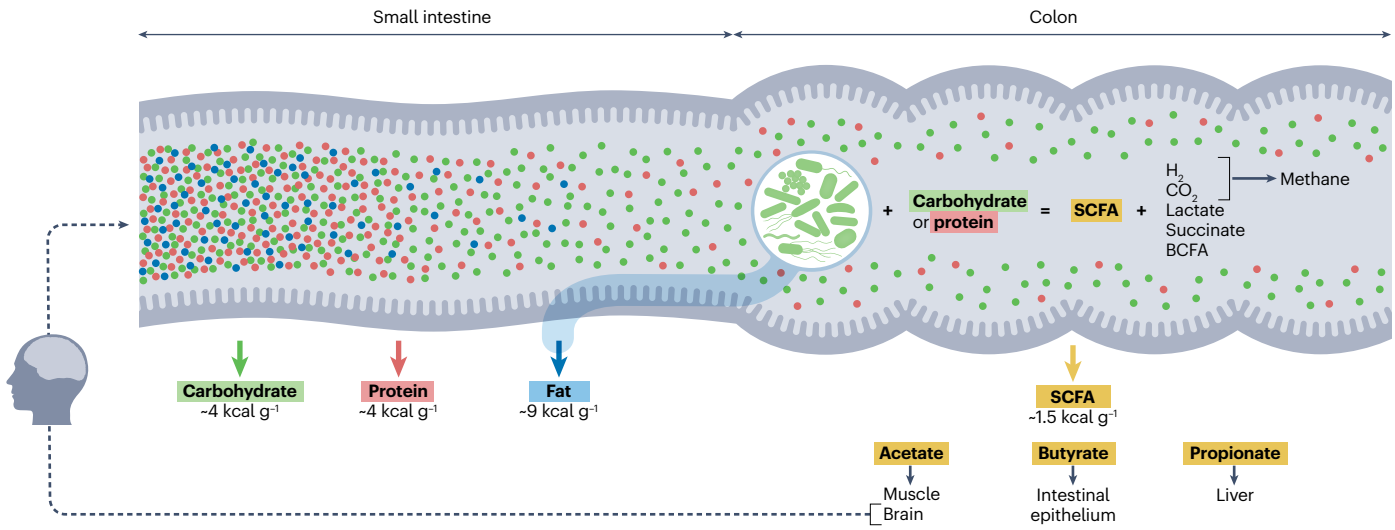

Fig. 2 | Gut microbiome enhances dietary energy harvest. Macronutrients available for breakdown by host enzymes are digested in the small intestine. Small intestinal macronutrient absorption supplies the host with energy predictable by biochemistry (carbohydrate, ~4 kcal g^{-1}; protein, ~4 kcal g^{-1}; fat, ~9 kcal g^{-1}). Dietary fat is readily absorbed in the proximal small intestine, and although fat digestion canonically depends exclusively on host enzymes, evidence of gut microbiome contributions to small intestinal lipid absorption in animal models[152,153] and host–microbial interactions in lipid emulsification[154] challenge this view. By contrast, it is well accepted that microorganisms augment carbohydrate and protein digestion. The fractions of carbohydrate and protein digested in the small intestine vary with macronutrient structural form (for example, higher for sugar versus fibre), meal composition (for example, higher for fibre-poor versus fibre-rich meals), thermal processing (for example, higher for cooked foods) and physical processing (for example, higher for smaller particle sizes)[155,156]. Nutrients that escape small intestinal digestion undergo fermentation by the colonic gut microbiota, producing an array of metabolites with energetic implications. The gut microbiome produces branched-chain fatty acids (BCFAs) from dietary valine, leucine and isoleucine, plus other organic acids such as lactate and succinate. However, undigested carbohydrates are the principal fuel for microbial fermentation, from which the gut microbiome generates the short-chain fatty acids (SCFAs) acetate, butyrate and propionate. These SCFAs are absorbed by the host and contribute to energy metabolism in diverse tissues, with acetate supporting muscle and brain, butyrate supplying up to 60–70% of the energetic needs of the colonic epithelium and propionate used in hepatic gluconeogenesis[157]. Energy returns from SCFAs have been estimated at ~1.5 kcal g^{-1} (ref. 157), less than half the rate for carbohydrates digested in the small intestine. Thus, more energy is harvested by the host when nutrients are digested directly versus fermented. Nevertheless, SCFAs account for ~5–10% of daily energy requirements in industrialized populations[158] and almost certainly a greater fraction in populations with minimally processed and/or fibre-rich diets[157]. Although SCFAs were long appreciated primarily as vehicles for energy salvage, recent research has shown that SCFAs possess potent signalling functions that modulate energy intake (dashed arrow; see also Box 1), energy utilization (Fig. 3) and inflammation (Box 2). These pleiotropic effects help explain why studies of high-fat diets with or without SCFA supplementation have reported inhibitory effects of SCFA on weight gain[159,160]. Host metabolites, including bile acids (Fig. 3) and immune factors (Box 2), also interact bidirectionally with the gut microbiome and influence its contributions to energy balance.

intake, decreased activity, a lower resting metabolic rate or reduced allocation to immunity or reproduction. Similarly, studies in mice and humans suggest that signals of delayed gut microbial maturation can precede the onset of malnutrition in infants[31]. What impairs gut microbial maturation is unknown, but decompartmentalization and small intestinal bacterial overgrowth have been proposed as contributing factors[32].

Remarkably, metabolic programming by the gut microbiome may even precede birth, as illustrated by a recent study in mice showing that SCFAs from the maternal microbiome cross the placental barrier and bind to GPR41 and GPR43 receptors in the developing embryo, affecting downstream tissue development[33]. Pups born to mothers harbouring microbiomes deficient in SCFA production owing to germ-free status, antibiotic treatment or low-fibre diets had higher risks of metabolic syndrome on encountering high-fat diets as adults than did pups born to mothers harbouring SCFA-producing microbiomes. Critically, pups born to both SCFA-deficient and SCFA-producing mothers were surgically delivered and cross-fostered, so this difference was not attributable to vertical inheritance of an SCFA-producing microbiome. Rather, it was the embryonic exposure to SCFA from the maternal microbiome that determined developmental fate and the future interaction of metabolic phenotype with diet. Similarly, recent data implicate fetal exposures to microorganisms[34] or vertical inheritance of perturbed maternal microbiomes[35] in shaping immune development. Although effects have not yet been investigated in humans, these murine data suggest that the microbiome could be a vehicle for intergenerational modulation of the efficacy of weight management interventions.

Gut microbial influences on energy metabolism can cast shadows over the life course and affect organs far beyond the gut (Fig. 4). The pleiotropy inherent in these diverse mechanisms helps to explain why it can be difficult to predict a priori the effect of gut microbial perturbations on host metabolic responses.

Diets and weight management

Cross-sectional microbiome-wide association studies have provided clear evidence that diet is an important determinant of gut microbiome[36,37]. Large cohort studies have demonstrated links between diet and microbiome composition and diversity[38,39]. Owing to the high degree of interindividual variation observed in human

microbiome studies, longitudinal analyses of short-term interventions have been particularly powerful in elucidating gut microbial responses to diet. Studies using this approach have addressed animal-based and plant-based diets[40], high-fat low-fibre and low-fat high-fibre diets[41], very-low-calorie diets[28] and high-fibre whole-food diets[42] and have observed diet-induced changes in as little as 1–2 days that were reversible after diet cessation[28,40] (Supplementary Table 1). Such diet-induced plasticity has been linked to success in sustained weight loss interventions[43], highlighting the promise of dietary manipulation of host–microbial interactions for weight management.

Dietary properties shaping gut microbial contributions to weight management

Weight management diets frequently manipulate dietary macronutrient content, as exemplified by low-carbohydrate, low-fat or high-protein programmes. There may be a false polychotomy between these diets as dietary composition is a zero-sum game, with a reduction in one proportion necessitating the rise in another. For instance, many studies have focused on dietary fat as a driver of microbial outcomes when, in fact, these diets have also differed in sugar and/or fibre content as well as whole-food versus semi-purified states[44,45]. Potential pitfalls of focusing on a given macronutrient are highlighted by recent reports that microbial responses to high-fat ketogenic diets and high-fat non-ketogenic diets are distinct, with ketogenic diets resulting in a loss of bifidobacteria, potentially owing to antimicrobial effects of ketones[46]. Moreover, common weight management diets are typically not isocaloric, but drive a reduction in caloric intake that itself can elicit similar clinical outcomes[47] and microbial responses (Supplementary Table 1).

However, some discrete properties of diet have received attention for their effects on the gut microbiome. Dietary fibre delivers fermentable substrate to the colon, enriching for microorganisms synthesizing carbohydrate-active enzymes and upregulating SCFA production[48]. Indeed, chronic low-fibre consumption led to extinction of these taxa

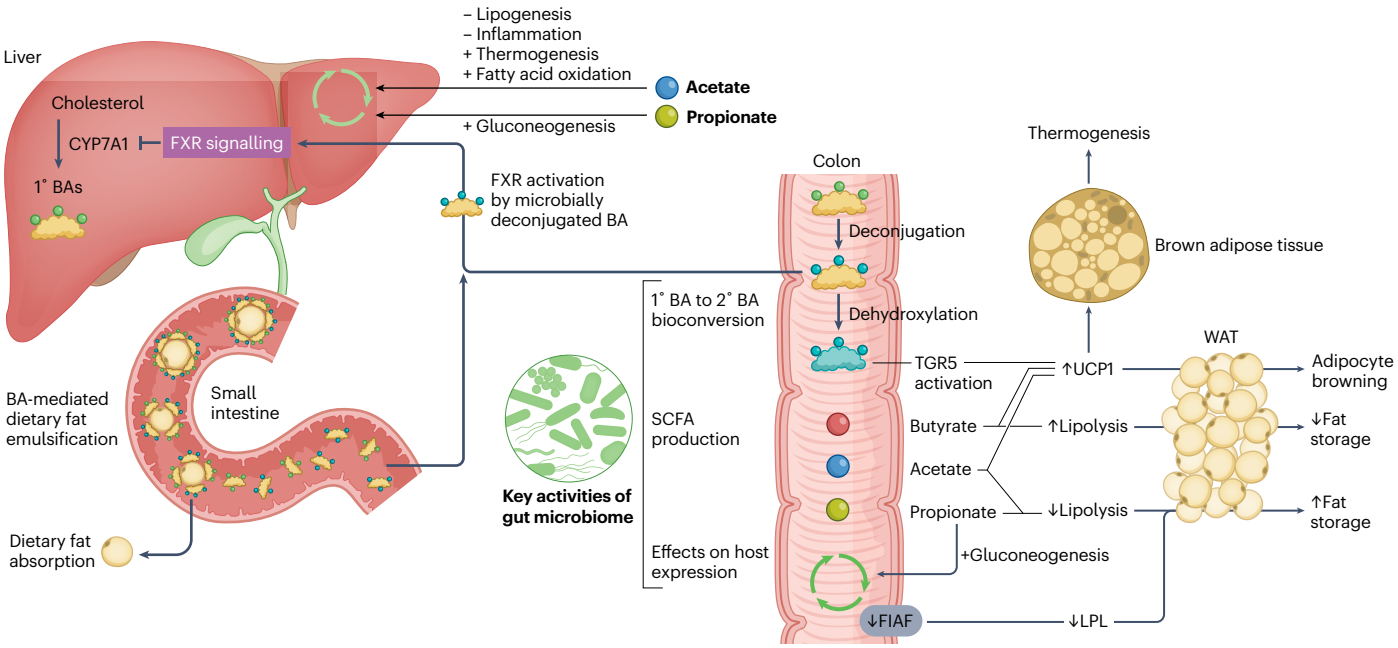

Fig. 3 | Gut microbiome modulates energy utilization. Signals from the gut microbiome act on adipocytes to direct whether available calories are allocated to storage or thermogenesis. Early animal experiments showed that gut microbial colonization leads to increased triglyceride storage in adipocytes through intestinal suppression of a circulating lipoprotein lipase (LPL) inhibitor, fasting-induced adipocyte factor (FIAF), leading to high cellular uptake of fatty acids[9]. Short-chain fatty acids (SCFAs) also affect the metabolic state of adipose, intestinal and hepatic tissue. Although definitively linking SCFA production to tissue status is challenging owing to inconsistent outcomes and designs across studies, intestinal utilization of SCFA by microorganisms and host, collateral changes in the microbiome and pleiotropic effects of SCFAs on physiology[12,161], many studies have found acetate, butyrate and propionate to exert differential effects. For instance, lipolysis in energy-storing white adipose tissue (WAT) was inhibited and fat accumulation promoted by acetate and propionate[162,163], whereas butyrate promoted lipolysis and fatty acid oxidation[164]. Butyrate enhanced thermogenesis in energy-consuming brown adipose tissue[165], whereas acetate and acetate-rich SCFA mixtures increased WAT browning[160]. Propionate promoted gluconeogenesis in the liver[166] and intestine[167], whereas hepatic acetate has been reported to reduce lipogenesis, limit fat accumulation, increase the expression of thermogenesis and fatty acid oxidation genes and reduce inflammation[168,169]. Moreover, a given SCFA compound can influence physiology in opposing ways in different tissues, as exemplified by acetate or butyrate supplementation increasing GPR43 expression in adipose tissue while reducing it in the colon[160]. Such differential effects raise the possibility that metabolic states could be manipulated via delivery of specific SCFAs. Gut microbial transformations of BAs also regulate energy metabolism. Gut microorganisms convert host-produced primary BAs (1° BAs) into secondary bile acids (2° BAs) via deconjugation and dehydroxylation. BAs transformed by the gut microbiota possess diverse signalling functions. For instance, deconjugated primary and secondary BAs are principal ligands for the nuclear farnesoid X receptor (FXR), a transcription factor with key regulatory roles in BA, cholesterol, lipid and glucose metabolism[170]. Through FXR signalling, microbial deconjugation of primary BAs can decrease hepatic expression of CYP7A1, the rate-limiting enzyme in primary BA synthesis[171], with potential downstream effects on lipid absorption in the small intestine[154]. Additionally, gut microbial BA metabolism has a critical role in regulating thermogenesis. Notably, the secondary BA lithocholic acid is a high-affinity agonist of the G protein-coupled receptor TGR5, inducing both WAT and brown adipose tissue thermogenesis via upregulation of uncoupling protein 1 (UCP1)[172].

Box 2

Interactions of the gut microbiome with low-grade inflammation

Chronic low-grade inflammation, characterized by aberrant cytokine production and persistent inflammatory signalling, is a central feature in metabolic syndrome. Unlike acute inflammation, which is a response to tissue injury, low-grade inflammation principally arises owing to metabolic surplus[188]. The gut microbiome has a key role in modulating low-grade inflammation. Bacterial exposures in the first years of life are critical for establishing systemic immunoreactivity, a topic explored in depth in recent reviews[189,190]. Throughout life, interactions between bacterial products (microbe-associated molecular patterns) and innate pattern-recognition receptors expressed in the intestinal epithelium, such as Toll-like receptors and NOD-like receptors, activate signalling pathways resulting in immune cell activation and inflammation. Although the mechanistic relationship between inflammation and energy metabolism remains incompletely understood[188], not all microbiota-dependent inflammatory responses have negative consequences for metabolic health. For instance, although exogenous delivery of lipopolysaccharide in mice triggered low-grade systemic inflammation eliciting obesity and insulin resistance[191], knockout of flagellin-sensing Toll-like receptor 5 in mice promoted obesity and insulin resistance with effects partially transmissible to wild-type gnotobiotic mice via microbiota transplantation[192].

Bacteria and pro-inflammatory bacterial compounds often trigger low-grade inflammation by entering circulation via faults in gut mucosal and epithelial cell barriers, a state colloquially referred to as 'leaky gut'[193]. Critically, the gut microbiome modulates gut barrier integrity. Gut microbiota conditioned on high-fat diets or dietary emulsifiers can transmit deficient mucosal phenotypes through transplantation, including reduced mucosal barrier thickness, bacterial encroachment towards epithelial cells and increased translocation of bacterial products into circulation[194]. By contrast, many bacterial taxa have been reported to have protective effects on gut barrier integrity. For instance, the mucin-degrading bacterium *Akkermansia muciniphila* has been shown to promote increased mucus barrier thickness and reduced translocation of lipopolysaccharide into circulation, contributing to reductions in high-fat diet-induced adiposity, adipose tissue inflammation and insulin resistance[12].

among mice[49]. In recent human studies, consumption of high-fibre diets increased microbiome-derived glycan-degrading enzymes[50] or known fermentative taxa[42], although effects on SCFA production, microbiota diversity and host phenotype varied[42,50]. Use of dietary fibre as an adjuvant to pharmacological treatment with acarbose, an α-glucosidase inhibitor used for type 2 diabetes, promoted growth of SCFA-producing microorganisms and decreased HbA1c levels, a biomarker of blood glucose[51]. Yet, effects of fibre supplementation have not been uniformly beneficial. For instance, administration of arabinoxylan or long-chain inulin, isolated fibres found in common over-the-counter weight-loss supplements, had differential effects on gut microbial and host phenotypes, with arabinoxylan lowering cholesterol and inulin promoting growth of bifidobacteria, but high inulin doses (30 g per day) eliciting inflammation and elevated liver enzymes[52]. Isolated fibre supplements typically target growth of bifidobacteria and lactobacilli[53] and therefore may not replicate the effects of a diet rich in diverse polysaccharides. However, because fermentable fibres are differentially capable of stimulating SCFA production[54], and SCFAs differ in their biological effects on energy metabolism at distal sites (Figs. 3 and 4 and Box 1), precision fibre interventions could potentially be used to engineer the composition of the SCFA pool to alter energy metabolism[55].

Additives such as emulsifiers and non-caloric artificial sweeteners (NAS) have become ubiquitous in industrialized diets. Although generally recognized as safe, recent studies have demonstrated that these compounds impact the gut microbiome and its contributions to energy metabolism[56–58]. Emulsifiers such as carboxymethylcellulose and polysorbate 80 have been observed to disrupt the intestinal mucosa, leading to microbiota encroachment, low-grade inflammation, adiposity and high blood glucose levels that are transmissible via microbiota transplantation[58]; however, relatively few well-powered studies are available to confirm these findings in humans[56]. Similarly, studies in animals and humans have indicated that NAS compounds such as saccharin and sucralose promote glucose intolerance, with dosing in the acceptable daily intake range leading to microbiota-transmissible weight gain, metabolic abnormalities and inflammation[57,59–61]. However, these results were not corroborated in follow-up animal experiments[62] or human studies involving saccharin and sucralose[62,63]. Such lack of reproducibility between groups and small human study sample sizes (<20 participants per intervention group)[57,61,62] indicates that further investigation and adequately powered double-blind, placebo-controlled studies will be required to establish any deleterious effects of NAS.

Fermented foods and probiotics are frequently suggested as promoting metabolic health, but empirical evidence is limited. Direct comparison of results between different fermented food and probiotic intervention studies is often difficult owing to variation in nutrient content and preparation, as well as the varying species and strain compositions used. Diets enriched in various fermented foods — for example, cheese, kefir, yogurt and kombucha — were recently shown to increase gut microbiome diversity and to reduce both pro-inflammatory and anti-inflammatory cytokines in serum[50]. However, owing to the lack of dietary standardization, it remains unclear which functional foods and their respective microorganisms were responsible for these effects. The immunomodulatory capabilities of conventional lactic acid bacteria-based probiotics are well documented[64], and there is emerging evidence for beneficial effects on glucose homeostasis[65,66]. However, evidence for their efficacy in weight modulation is limited, with few high-quality studies available[67,68]. Yogurt consumption has been associated with lower weight, weight gain, body mass index, waist circumference and body fat in a systematic review, but cause–effect relationships remain unclear owing to confounding variables[69]. Treatment for 12 weeks with *Lactobacillus sakei*, a probiotic isolated from kimchi, led to reductions in body fat and waist circumference but no effects on body weight or body mass index in a recent randomized, double-blind, placebo-controlled study in humans with obesity[70]. Despite robust product marketing, to our knowledge, no high-quality

evidence currently links kombucha to either immune or metabolic benefits in humans[71].

Specific diets and gut microbial contributions to weight management

Diet is a complex variable with many dimensions affecting microbiome composition, including caloric content, macronutrient and micronutrient load, preparation and timing of feeding. Although each dimension can be studied in isolation in controlled human or animal studies, weight management diets typically incorporate combinations of these variables, making it challenging to decipher their respective contributions. This is further complicated by difficulties inherent in the direct comparison of microbiome data across studies and in comparing microbiome signatures across individuals. To quantify high-level effects of weight management interventions on the human gut microbiota, we used a previously published method[44] to compare intra-individual microbiota changes in 14 longitudinal studies addressing common weight management interventions including caloric restriction, nutrient modulation, exercise and RYGB surgery (Supplementary Methods). Studies were selected on the basis of design and data availability (Supplementary Table 2). Consistent with previous reports, we found that α-diversity was neither a robust nor reproducible indicator of intervention. However, gut microbiota composition was reproducibly altered by weight management intervention across participants in 12 of 14 studies (Fig. 5a). An important consideration in interpreting this result is that effects of weight management intervention are unlikely to outweigh effects of

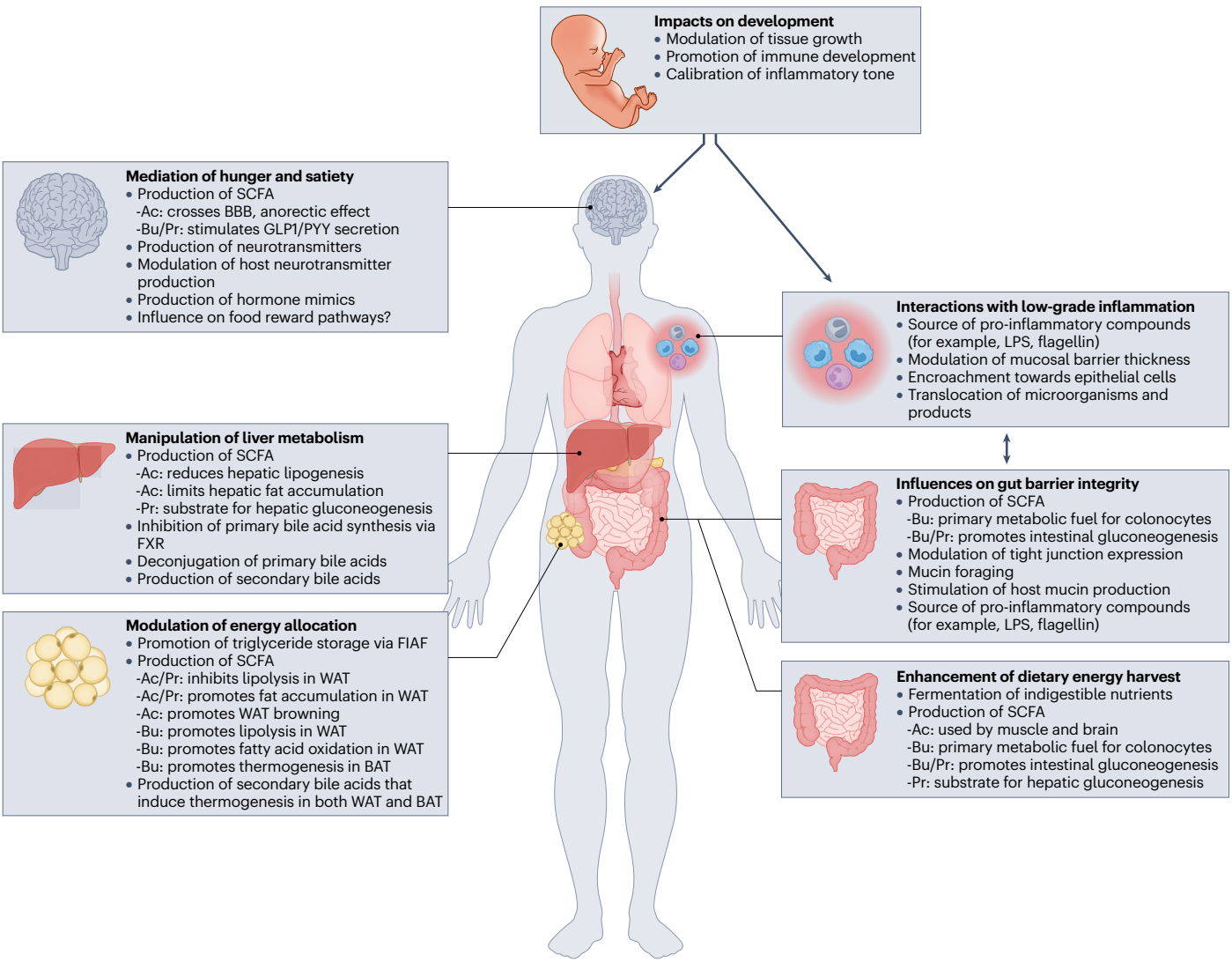

Fig. 4 | Mechanisms of gut microbial influence on host energy status. The gut microbiome contributes to host energy metabolism through early-life influences that shape metabolic and immune physiology, as well as dynamic influences throughout life on hunger and satiety, dietary energy harvest, bile acid metabolism and allocation of available energy to storage versus thermogenesis (Box 1 and Figs. 2 and 3). In addition, the gut microbiome modulates interactions between energy metabolism and low-grade inflammation through its calibration of inflammatory tone in early life, production of pro-inflammatory compounds and modulation of gut barrier integrity (Box 2). Ac, acetate; BAT, brown adipose tissue; BBB, blood–brain barrier; Bu, butyrate; FIAF, fasting-induced adipocyte factor; FXR, farnesoid X receptor; GLP1, glucagon-like peptide 1; LPS, lipopolysaccharide; Pr, propionate; PYY, peptide YY; SCFA, short-chain fatty acid; WAT, white adipose tissue.

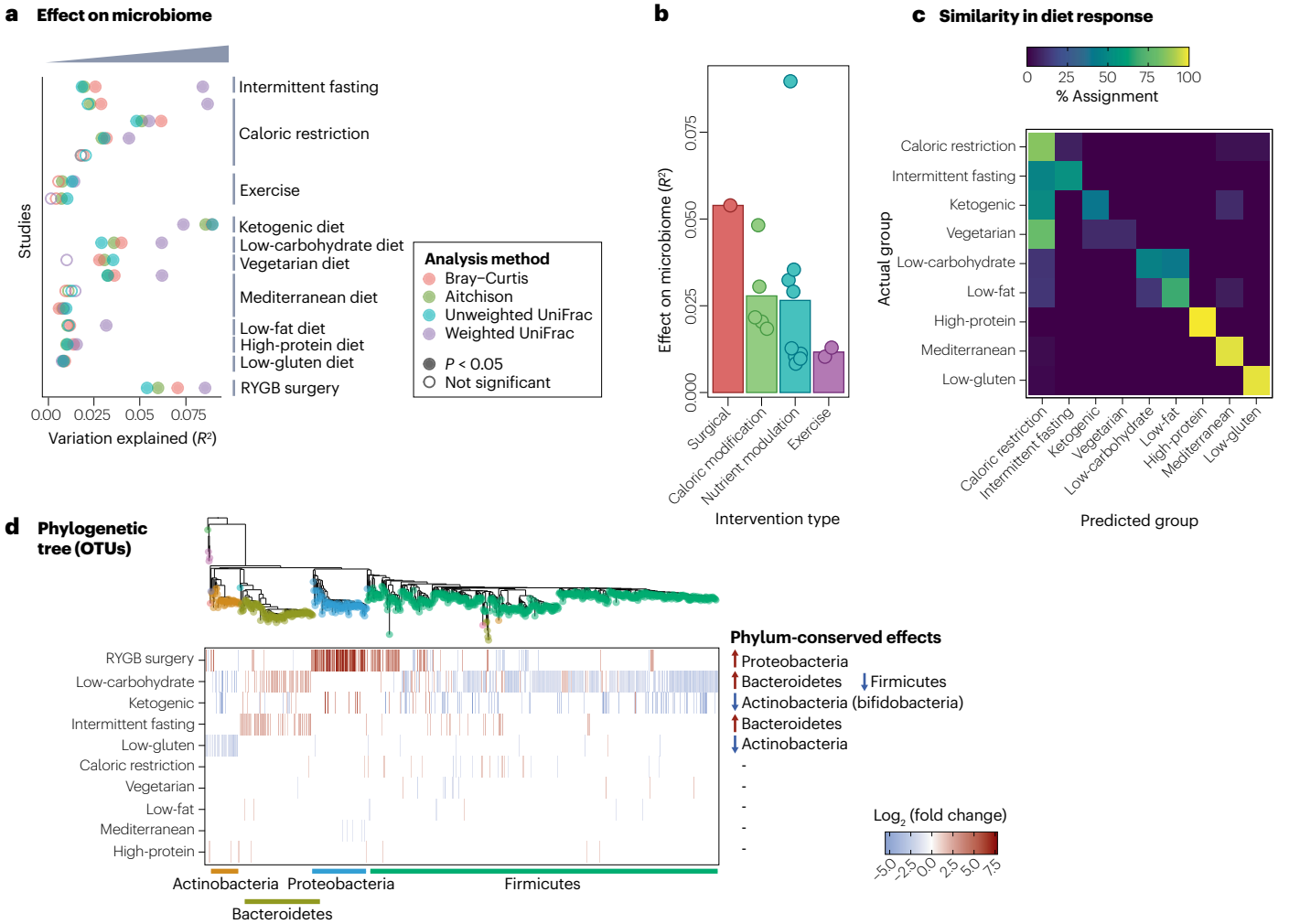

Fig. 5 | Meta-analysis of the effects of weight management interventions on gut microbiome composition. a, Interventions have variable magnitudes of effect on the gut microbiome as measured by the proportion of variation in gut microbiome composition attributed to intervention within each study, a metric that is robust to how differences in microbiome composition are measured across studies. The panel illustrates results for several of the most common distance metrics used to characterize sample-to-sample differences, including Bray–Curtis dissimilarity, Aitchison distance, Unweighted UniFrac distance and Weighted UniFrac distance. Differences in the results obtained for different distance metrics reflect their variable treatments of relative abundance and phylogenetic relationships. **b**, Surgical interventions and dietary interventions tend to display greater effects than exercise in modulating the microbiome, as measured by the proportion of variation explained. The panel illustrates an analysis of Unweighted UniFrac distances, but similar results were observed using other common distance metrics. Caloric modification diets were inclusive of intermittent fasting and diets aiming to reduce caloric intake, whereas nutrient modulation diets included diets involving intentional rebalancing of macronutrients (for example, low-carbohydrate, low-fat, high-protein or ketogenic diets) and Mediterranean diets. **c**, To determine similarity in gut microbial response to various diets, a machine learning model was fit to the data. This model demonstrated that high-protein, Mediterranean and low-gluten diets have distinct, readily distinguishable effects on the gut microbiome (indicated by yellow squares). By contrast, the effects of intermittent fasting, ketogenic and vegetarian diets were difficult to separate from general caloric restriction, and the effects of low-carbohydrate and low-fat diets were difficult to distinguish from each other (indicated by blue-green squares). **d**, Analysis of organisms (operational taxonomic units (OTUs)) affected by weight management interventions and ordered horizontally by their phylogenetic relatedness revealed conserved effects of diet at the phylum level. Specific phylum-level associations are listed to the right of the figure. RYGB, Roux-en-Y gastric bypass. Details of the studies contributing to this meta-analysis are given in Supplementary Table 2 and Supplementary Methods.

interindividual variation. Although not always reported, we determined that intervention explained 0.6–9.0% of variation in gut microbiota composition, whereas interindividual variation explained 55.2–87.0%, depending on the study design and distance metric.

Intervention durations varied widely in our dataset, spanning 3 days to 12 weeks. Notably, we did not detect a significant correlation between effect size and intervention duration, regardless of distance metric (rho = −0.09 to 0.2, all $P > 0.43$, Spearman correlation), reinforcing the idea that even short-term lifestyle interventions can reprogramme the gut microbiome[40,72]. Interstudy comparison of effect sizes revealed that RYGB surgery exhibited the greatest effect on microbiome composition, followed closely by caloric restriction, nutrient

Glossary

α-Diversity
Diversity of microbial taxa within a given sample; distinct from β-diversity, which indexes differences in microbiome composition between samples.

Energy balance
The balance between energy intake and expenditure crucial in weight maintenance.

Faecal microbiota transplantation
(FMT). The experimental or therapeutic administration of preparations of faecal material intended to transfer microbiota-mediated effects to a recipient.

Germ-free animals
Animals lacking resident microorganisms, which may be derived through sterile surgical birth followed by rearing and propagation under strictly sterile conditions.

Gnotobiotic mice
Animals born without microorganisms (that is, germ-free) that may be colonized to study effects of microbial colonization on host physiology.

Gut barrier
Multilayered structure (consisting of mucus with embedded antimicrobial peptides and secretory IgA, epithelial cells and their cell-to-cell junctions, and the immune element-rich lamina propria) that simultaneously allows for nutrient absorption while restricting contact with the gut microbiota and its products.

Ketogenic diet
A protein-adequate diet marked by high-fat and very-low (<10% kcal) carbohydrate intake that forces the metabolism of stored fat into ketones.

Low-grade inflammation
Immunometabolic state, marked by the chronic production of low-level inflammatory factors, that bidirectionally potentiates metabolic disease.

Mediterranean diet
A diet emphasizing plant-based ingredients and unsaturated fats (mainly olive oil), moderate amounts of seafood and poultry and minimal amounts of refined carbohydrates and red meat.

Meta-analysis
Analysis using the data derived from multiple studies to achieve greater sample size and uncover reproducible findings.

Metabolic syndrome
A cluster of physiological conditions — including excess visceral fat, high fasting glucose, high triglycerides, low HDL cholesterol and/or high blood pressure — that can together increase the risk of diabetes, heart disease and stroke.

Microbiome
The genetic content and products of a community of microorganisms.

Microbiome diversity
Measurements of the number of microorganisms/genes present within an individual and/or how evenly they are distributed.

Microbiome-wide association studies
Studies employing a statistical approach that mines microbiome and host phenotype datasets to identify specific microbial taxa or microbial genes that are associated with specific host traits; also known as metagenome-wide association studies.

Microbiota
A community of microorganisms inclusive of bacteria, fungi, viruses, archaea and protists.

Roux-en-Y gastric bypass
(RYGB). Bariatric surgery promoting weight loss, in which a small pouch of stomach is connected to the jejunum, thereby restricting food intake and bypassing digestion in the duodenum.

Short-chain fatty acid
(SCFA). Microbial metabolite resulting from fermentation with wide-ranging effects on host physiology.

Undernutrition
A state of deficient energy intake characterized by stunting (low height-for-age), wasting (low weight-for-height) and/or underweight (low weight-for-age) that increases the risk of morbidity and mortality, especially in children.

modulation and finally exercise (Fig. 5b). These classifications are necessarily imperfect as RYGB surgery in part targets caloric restriction, nutrient modulation can affect caloric load and exercise often alters diet. A subanalysis of dietary interventions revealed that intermittent fasting, prolonged caloric restriction and ketogenic diets had the greatest effects on gut microbiota composition, with diets identified as vegetarian or low gluten having the least effects (Fig. 5a). To understand which diets elicited similar effects, we used machine learning methods to predict diet type from diet-induced change in gut microbial composition (Supplementary Methods). We found that the model struggled to differentiate intermittent fasting, ketogenic and vegetarian diets from caloric restriction, whereas high-protein, Mediterranean and low-gluten diets were easily distinguished (Fig. 5c). Phylogenetic examination of the microorganisms responsive to intervention (Fig. 5d) demonstrated both high-level signals, such as increases in Proteobacteria after RYGB surgery or in *Bacteroides* spp. after intermittent fasting or low-carbohydrate diets, but idiosyncrasy within and between diets. Although comparisons should be interpreted cautiously as the number of available studies for any given intervention is low, and the nature of sequencing does not capture reductions in microbiota absolute abundance as previously identified for very-low-calorie diets[28], these observations offer a first glance into the comparative gut microbial effects of weight management interventions.

Diet outcomes

One of the great opportunities in translating microbiome science lies in using the microbiome as a prognostic tool. The high degree of interindividual variation in short-term and long-term response to weight loss interventions has been linked to various behavioural and biometric predictors, but the microbiome may offer new biomarkers for intervention efficacy and long-term weight maintenance. Proof-of-principle data in mice demonstrated that classifier models exploiting microbiota composition predicted weight regain in a 'yo-yo' dieting paradigm with high accuracy[23]. Specific microbial taxa have also been linked to diet efficacy. For instance, baseline levels of *Prevotella* spp. predicted 6-week weight loss on a high-fibre, whole-grain diet[73], and higher gut microbiota diversity and relative abundance of taxa such as Ruminococcaceae spp. and Lachnospiraceae spp. predicted weight gain over a 10-year period among healthy females from the TwinsUK cohort[74]. In a recent study, it was determined that ~22–38% of change in body fat during weight loss intervention could be explained by the baseline microbiota, with certain Clostridia and *Parabacteroides* spp. indicative of increased loss[75]. Interestingly, elevated baseline microbiota diversity has been correlated with lower fat loss, reinforcing the idea that the pursuit of high gut microbiota diversity is unlikely to be uniformly beneficial[76,77]. Microbiome composition, when integrated with anthropometric and lifestyle indicators, was also shown to

improve the prediction of postprandial glycaemic response to a given meal, with Proteobacteria linked to poor response[78]. Individuals differ widely in their responses to diet[79], and determinants of this variation have remained elusive. Such studies offer the tantalizing notion that diets could be tailored to the microbiome of an individual to maximize clinical efficacy.

Physical activity and weight management

Similar to diet, physical activity is a key lever for weight management that impacts the gut microbiome through diverse pathways. Although diet can shape the gut microbiome directly by altering the luminal nutritional milieu, effects of physical activity on the gut microbiome are mostly indirect. Correspondingly, effect sizes of physical activity on gut microbiota composition are typically lower than those of diet[80–82] (Fig. 5b).

Gut microbiota composition is sensitive to both acute and chronic physical activity in rodents[83,84]. However, gut microbial signatures of exercise have differed widely across studies, presumably owing to differences in exercise type and intensity, diet, species and/or strain, age and other elements of study design. Even voluntary wheel running versus forced treadmill exercise differentially alters the gut microbiome in mice[84]. Relatively reproducible among effects reported to date is that of voluntary wheel running on the gut microbial capacity for butyrate production, including higher abundances of butyrate-producing taxa and/or increased faecal or caecal concentrations of butyrate in exercised animals versus sedentary controls[85].

The gut microbiome also differs between active and sedentary humans[81,86–88]. The gut microbiome of human endurance runners and more sedentary controls differs at baseline and dynamically changes within individual runners during a distance race[87,88], with enrichments of *Veillonella*[87] and Coriobacteriaceae[88] taxa of particular interest. Similarly, elite rowers and ultramarathoners experience changes in the microbiome before versus after exercise[87], rugby players exhibit distinct gut microbial taxonomic and functional signatures compared with more sedentary individuals[89,90] and modest differences in the microbiome have been detected between professional and amateur competitive cyclists[91]. Several studies have reported correlations between gut microbiome structure and function and cardiorespiratory fitness, as assessed by oxygen uptake ($\dot{V}O2_{max}$ or $\dot{V}O2_{peak}$)[92,93]. In addition, several studies have found increases in SCFA concentrations and/or butyrate-producing taxa in athletes compared with more sedentary individuals[90] and in individuals with higher versus lower cardiorespiratory fitness[93], consistent with data from animal models suggesting that exercise enriches the gut microbiome for SCFA production. A recent study reported that the absolute abundance of SCFA-producing *Bacteroides uniformis* was correlated with 3,000-m race time, and dietary interventions targeting its abundance led to increased performance that could be replicated by administration of *B. uniformis* to mice[94]. Similarly, individuals with prediabetes who harboured microbiotas with higher basal capacity for SCFA production saw greater improvements in glycaemic response after a 12-week high-intensity exercise intervention[95]. Moderate activity also seems to affect gut microbiota composition in similar ways, with active women harbouring increased levels of two butyrate producers, *Faecalibacterium prausnitzii* and *Roseburia hominis*, and metabolism-modulating *Akkermansia muciniphila*[96,97] (Box 2).

However, the extent to which these differences are confounded by body composition and other lifestyle factors such as diet remains unclear[81,88,98]. Indeed, increased daily protein intake of elite rugby players versus more sedentary individuals accounted for many of the observed intergroup differences in gut microbiota composition[89]. The handful of studies incorporating rigorous dietary control have reported differential and plastic gut microbial responses to physical activity. For instance, among previously sedentary adults exposed to 6 weeks of supervised, endurance exercise with a standardized 3-day dietary intervention implemented before sample collection, changes in the gut microbiome at intervention end-point differed on the basis of the baseline host phenotype[86]. Exercise increased faecal butyrate and acetate concentrations and the relative abundance of butyrate-producing taxa in participants who were lean but not in participants who were obese. Similarly, exercise increased *Faecalibacterium* spp. in participants who were lean but had opposite effects in participants who were obese. Changes in the microbiome at the intervention end-point were largely reversed following a 6-week sedentary washout period, suggesting that the gut microbiome responds dynamically to exercise input.

The mechanisms through which physical activity affects the gut microbiome have not been elucidated, but physical activity alters the gut luminal environment in diverse ways. For instance, exercise alters cytokine expression in intraepithelial lymphocytes[99], which have a critical role in mediating host–microbial interactions within the intestinal mucosa[100]. Exercise may have hormetic effects on gut barrier integrity, with intensive exercise leading to short-term increased permeability[101] but routine exercise promoting reduced permeability, as evidenced by highly trained athletes having lower circulating lipopolysaccharide levels compared with more sedentary individuals[102]. Among hypercholesterolaemic mice, voluntary wheel running increased primary bile acid secretion and faecal excretion[103], suggesting that exercise may mediate bile acid metabolism. During anaerobic exercise, circulating lactate may translocate into the gut lumen[87] and alter luminal pH. Exercise increases reactive oxygen species production as well as antioxidant enzyme activity, and studies involving genetic and pharmacological manipulation of reactive oxygen species have reported impacts on gut microbiota diversity[104]. Exercise increases gut motility and reduces colonic transit time[105], which is associated with an altered microbiota composition[106]. Physical activity also transiently raises core temperature, induces short-term restrictions to intestinal blood flow[107], alters endocrine signalling[108], generates mechanical forces and alters food and water consumption in ways expected to influence competitive interactions within the gut lumen.

Whether these exercise-induced changes in the gut microbiome alter gut microbial contributions to energy metabolism remain unknown. One challenge is the diversity of responses across hosts, such that even studies detecting effects of exercise on the gut microbiome can report no cohort-wide differences in metabolism, possibly because of responder and non-responder effects[97]. The most apparently reproducible effect of exercise on the gut microbiome across human and animal studies, higher butyrate production, might be expected to increase gut barrier integrity and thereby reduce low-grade inflammation, conferring metabolic benefits in cases of overnutrition. It is notable, therefore, that high-fat diet-fed obese mice receiving faecal transplants from control diet-fed exercised donors exhibited weight loss, lower expression of pro-inflammatory cytokines in liver and lower fasting blood glucose levels, in combination with enrichment in butyrate-producing taxa[80]. However, the extent to which these improved metabolic parameters were due to exercise versus diet versus donor health status is uncertain, as transplants from control diet-fed exercised donors elicited more beneficial outcomes than transplants from high-fat diet-fed exercised donors, the study did not include

a control diet-fed non-exercised donor treatment, and the authors reported that diet generally had a stronger effect on the gut microbiome than did exercise[80]. Studies isolating the energetic consequences of exercise-induced changes in the gut microbiome are especially needed and will enrich our knowledge of available lifestyle levers for microbiome-directed weight management.

Clinical paths and weight management

When diet, exercise and other behavioural interventions prove insufficient, clinical intervention may be required to manage weight and related sequelae. In this section, we discuss interactions between medical interventions and the gut microbiome as well as microbiome-targeted clinical therapies for weight management.

Surgical approaches

Surgical treatments for severe obesity aim to reduce food intake and/or decrease nutrient absorption[109]. These interventions have been reproducibly shown to increase microbiota richness (a measure of α-diversity) as well as increase the relative abundance of Proteobacteria (Enterobacteriaceae) and *Akkermansia* spp.[110–112] (Supplementary Table 2). These intervention-associated changes in microbiota composition have been functionally linked both to shifts in microbial metabolism[112] and to host health through the demonstration of reduced adiposity among gnotobiotic recipients of post-intervention gut microbiota compared with a control microbiota[113]. Unfortunately, there is evidence that the effects of surgical intervention on the microbiome may be short-lived, with substantial reversion within 1 year post-intervention[114]. Although surgical approaches such as RYGB tend to be highly effective overall, there is a subset of patients who exhibit a poor initial response or will regain weight following their surgery[115]. Current evidence that the gut microbiome contributes to variable post-RYGB responses is equivocal[116,117], with studies concurring that gut microbiota composition differs only modestly between individuals experiencing successful and poor weight loss outcomes. Nevertheless, faecal transplants from human post-RYGB patients to antibiotic-treated mice demonstrated that recipient weight gain phenotypes tracked donor outcomes[117], illustrating that the gut microbiota participates to some extent in weight loss success. Significantly higher levels of *Barnesiella* spp. were observed among humans experiencing poor weight loss outcomes and their murine gnotobiotic recipients, but further experiments are required to evaluate reproducibility and causal links. Although research is at an early stage, available data suggest that the microbiome can modulate surgical success to some extent, raising an important but unanswered question: could we one day mimic the effects of surgery through precision modification of the gut microbiome alone?

Drugs

Interindividual variation in drug response is a major challenge in medicine and is likely mediated in part by the gut microbiome[118]. There are multiple mechanisms through which this may occur, including direct interactions between gut microorganisms and oral drugs, off-target antibacterial effects of common drugs on the gut microbiome[119] and effects of drugs on host physiological systems interacting with the gut microbiome[118]. Although this nascent field is rapidly expanding, its importance to weight management and metabolic health is clear.

Perhaps, the best-known example of drug–microbiome interactions in metabolic health involves metformin, a first-line therapy for type 2 diabetes. Remarkably, transplantation of metformin-treated human donor faeces into germ-free mice was capable of improving glucose tolerance when compared with pre-treatment donor faeces, providing strong evidence that the gut microbiome contributes to drug efficacy[120]. Although metformin is well tolerated and widely used, approximately 30% of metformin-treated patients will experience gastrointestinal side effects that have been correlated with the intestinal abundance of *Escherichia coli*[121]. Alternatively, the α-glucosidase inhibitor acarbose has considerable off-target effects on the gut microbiota[122]. A highly prevalent microbial acarbose resistance mechanism resulting in drug inactivation has recently been identified, although its significance to drug efficacy remains to be determined in prospective studies[123].

Statins are commonly prescribed for the prevention and control of cardiovascular disease and target HMG-CoA reductase, which is involved in cholesterol biosynthesis. Across more than 3,000 participants in 3 cohorts, statin use was negatively associated with an inflammation-promoting microbiota signature characterized by a high proportion of *Bacteroides* spp., a low proportion of *Faecalibacterium* spp. and low absolute microbial cell density[124]. These findings were recently replicated and expanded to show that microbiota composition is capable of predicting treatment responses, with a *Bacteroides* species-enriched, low-diversity microbiota associated with not only increased adverse outcomes but also increased therapeutic effects[125]. Lower therapeutic benefits of statins among individuals with higher baseline gut microbial diversity were found even after correcting for the possibility that individuals harbouring higher gut microbial diversity are healthier and/or prescribed less-potent statin doses[125], suggesting that higher gut microbial diversity itself may hamper drug efficacy.

Faecal microbiota transplantation and other restoration approaches

Many organisms harbour redundant capacities for modulating metabolic health, raising hopes of therapeutic manipulation via the transfer of whole microbial communities through faecal microbiota transplantation (FMT). FMT has proven effective in combating recalcitrant infection by *Clostridioides difficile*[126] and has shown promise in inflammatory bowel disease[127]. However, results of FMT for weight management and obesity in humans have been mixed, ranging from no clinical effect[128] to positive effects on secondary outcomes such as reduced abdominal adiposity[129] and increased insulin response when coupled to diet intervention[130]. A recent study examined whether FMT could be used to maintain weight loss after lifestyle-based intervention through transplant of the microbiome of an individual at their point of maximal weight loss[131,132]. Patients with obesity or dyslipidaemia underwent a 6-month period of lifestyle-driven weight loss through exercise guidance and consuming either a healthy diet, Mediterranean diet or green-Mediterranean diet (Mediterranean diet plus green tea and *Wolffia globosa*-based shake)[131]. For the subsequent 8 months, participants were given either capsules containing autologous faeces collected at the end of the 6-month weight-loss phase or placebo. Only the green-Mediterranean diet group experienced significant changes in the gut microbiome during the weight-loss phase and, correspondingly, only in the green-Mediterranean group did autologous FMT attenuate weight regain, waist circumference gain and insulin rebound versus placebo[131,132]. Such data suggest that whole community replacement approaches are unlikely to be effective as a standalone solution, especially as autologous FMT circumvents some of the broader safety and ecosystem-matching challenges of heterologous FMT and therefore in many ways represents a best-case scenario.

Alternatively, microbiome restoration could be accomplished in more targeted ways that harness defined sets of microorganisms or microbial products robustly associated with health. Although the effects of traditional probiotics and prebiotics based on lactobacilli and bifidobacteria seem to have limited effects on weight or glucose homeostasis[65–68,70], new candidates are under active development. For instance, administration of pasteurized *A. muciniphila* in animal models seems safe and can protect against diet-induced obesity, insulin resistance and low-grade inflammation through positive effects on gut barrier integrity[133]. Correspondingly, a recent exploratory human study with 40 participants found that daily oral administration of 10^{10} pasteurized *A. muciniphila* over a 3-month period was well tolerated, significantly reduced insulin resistance and insulinaemia and was associated with nonsignificant reductions in body fat and hip circumference versus baseline ($P = 0.09$)[134]. The finding that the efficacy of pasteurized *A. muciniphila* is higher than that of live bacteria[133] improves safety and ensures longer shelf-stability. In addition, recent discoveries that efficacy may be driven by the outer membrane protein Amuc_1100 (ref. 133) or secreted protein P9 (ref. 135), with additional benefits for homeostatic immunity through effects of the phosphatidylethanolamine a15:0-i15:0 (ref. 136), provide targets for drug development and the prospect of more predictable dosing kinetics, illuminating a path for translating basic discoveries into the clinic.

Towards microbiome-aware weight management

Key advances in our understanding of the influences of the gut microbiome on energy metabolism have been made in animal models, especially mice, that differ from humans in several aspects of anatomy, physiology, behaviour as well as microbiome structure and function[137]. Therefore, realizing the therapeutic promise of the gut microbiome in ameliorating metabolic dysfunction will require substantial translational research. Intensified challenges in humans compared with animals models include high degrees of interindividual variation and longitudinal resilience in the human gut microbiome[13,138], a low degree of ecological control driving day-to-day variation of the gut microbiome around these long-term signatures[139] and developmental plasticity exerting its influence over an extended human lifespan, resulting in greater temporal disconnect between host phenotypes and contributory microbial signatures. Developing protocols and synthetic microbial communities that can enable animal hosts to more faithfully replicate human–microbiome interactions in energy metabolism will be critical in narrowing the translational gap. It will also be useful to supplement murine studies with gnotobiotic studies in larger animals such as pigs, which more closely mimic humans in aspects of life history, physiology and the microbiome. In vivo approaches, especially those involving bioreactors designed to model physiological conditions in the human gut[140], and ex vivo approaches, such as organoids derived from induced pluripotent stem cells or biopsied tissue[141], are important complementary tools that have the benefit of greater control and reproducibility.

Difficulties in stably manipulating the human microbiome across individuals and environments suggest that one-size-fits-all and unrefined brute force approaches such as FMT are unlikely to be durably successful. Rather, greater long-term impacts will likely be achieved through personalized interventions targeting particular gut microbial functions and metabolites. In doing so, we will need to remain mindful of the pleiotropic effects of bacterial products. For instance, SCFAs participate in colonic energy salvage while also minimizing hunger, increasing thermogenesis and regulating embryonic tissue development (Figs. 2–4), raising the possibility that SCFA-based interventions could have complex, even intergenerational[33], outcomes. Confronting these challenges will enable rational manipulation of the gut microbiome to be sufficiently long lasting to improve health and either generalizable across individuals or personalized in an equitable manner.

We anticipate that within the next 10 years, many of the microbiome-modulating levers at our disposal will be revealed. Ongoing technical improvements in strain-level identification, culturing, genome editing and metabolite identification will enable us to characterize with greater specificity the microbial players of interest and the ecological conditions that encourage their presence. For instance, recent studies have discovered substantial whole-genome divergence among *A. muciniphila* strains, despite homogeneity in their 16S rRNA gene sequences[142] that may contribute to explaining why strains exhibit differential impacts on inflammation[143]. Continued delineation of the mechanisms through which the microbiome manipulates energy balance is expected to highlight promising targets for intervention in pathways regulating hunger and satiety, dietary energy harvest, energy allocation and interactions between energy metabolism and inflammation. For instance, leveraging information about the thermogenic effect of secondary bile acids via TGR5-mediated activation of brown adipose tissue (Figs. 3 and 4), it was recently discovered that weight rebound after caloric restriction could be suppressed by supplementing mice with non-12α-hydroxylated bile acids or *Parabacteroides distasonis*, a bacterium capable of producing these acids[22]. In addition, rapidly advancing knowledge of bacterial chemistry, including pervasive reciprocal interactions between the gut microbiome and therapeutic drugs[118,144], could suggest new microbiome-targeted approaches for enhancing the efficacy of existing drugs by potentiating or inhibiting bacterial biotransformations. Emergent knowledge of bacterial xenobiotic metabolism could eventually shape clinical decisions with regard to drug choice, dosage and/or coadministered agents, as has been proposed for non-metabolic drugs such as digoxin, irinotecan and levodopa[145–147]. By contrast, advances in our knowledge of small intestinal and mucosa-associated microbiota are proceeding more slowly, hampered by the greater invasiveness required in procuring such samples. Nevertheless, it is likely in the small intestine, where hosts and microorganisms compete directly for nutrients, and in the mucus layer, where host tissues and microorganisms come into closest proximity, that interactions are most consequential for energy metabolism and inflammation. Greater attention to these microbial communities is likely to reveal additional, high-impact targets for modulation.

Most research to date has focused on overweight and obesity rather than undernutrition. Yet existing evidence suggests that disruptions of the gut microbiome precede the onset of childhood malnutrition[31], correlate with the severity of wasting[26] and stunting[148] and transmit weight loss phenotypes to gnotobiotic mice on transplantation[25]. Such data suggest a pivotal role for the gut microbiome in undernutrition and ripe opportunities for the development of microbiome-focused therapies to ameliorate health for the one-in-three children worldwide who suffer from stunting and/or wasting.

Although much remains to be discovered, promising microbiome-focused clinical trials targeting metabolic phenotypes associated with undernutrition or overnutrition are currently underway. For instance, researchers recently developed several microbiota-directed complementary food (MDCF) recipes that were evaluated for their ability to mature the gut microbiome of undernourished Bangladeshi children to a healthy post-weaning profile[149,150]. The lead MDCF prototype subsequently showed improved efficacy versus standard ready-to-use therapeutic foods in Bangladeshi toddlers with moderate

acute malnutrition, eliciting significant relative improvements in weight-for-length and weight-for-age *z*-scores and changes in plasma proteins affecting bone growth and neurodevelopment[151]. Similarly, as discussed earlier, a recent study found that diet was an important support for the efficacy of autologous FMT in attenuating weight regain among patients with obesity or dyslipidaemia who had undergone a 6-month period of lifestyle-driven weight loss, as FMT was only beneficial when combined with a specific green-Mediterranean diet[131]. As with MDCF, these data indicate the potential for diet to act as an adjuvant for microbiome-targeted therapies. Future human trials of microbiome-targeted therapies should aim to standardize diet among participants by providing a fixed composition containing substrates to support microbial engraftment and the growth of beneficial microorganisms. Greater attention to dietary processing will also help to standardize delivery of nutrients to the densest microbial community in the colon[29]. Notwithstanding, diet-independent routes of manipulation are also showing promise, as exemplified by a study reporting that probiotic administration of pasteurized *A. muciniphila* or delivery of specific *Akkermansia*-derived effector molecules, such as Amuc_1100, can reduce adiposity and insulin resistance[134]. Collectively, such trials serve as important proofs-of-concept, showing that microbiome-aware therapies can compare favourably to and complement existing weight management schemes.

Outlook

Undernutrition and overnutrition weigh too heavily on public health not to leverage emerging transformational knowledge of gut microbial contributions to energy metabolism. Rational manipulation of the microbiome could increase the efficacy of existing therapies and generate novel treatments, giving physicians and patients new options for weight management. Several fundamental challenges will need to be overcome to realize this promise, including grappling with the ecological sensitivity of the gut microbiome, interindividual variability, developmental plasticity and pleiotropic effects of the gut microbiome on human physiology. However, successes of recent clinical trials targeting both undernutrition and overnutrition highlight that microbiome-directed interventions for weight management are on the near-term horizon. Increased focus on the function and products of the gut microbiome rather than composition, enhanced efforts to establish the translational significance of discoveries made in animal models and basic research to understand the physiological and ecological drivers of inflexion points where the microbiome switches between phenotypic buffering and exacerbation are needed to effectively leverage the microbiome in the ongoing fight to improve global metabolic health.

Published online: 3 May 2023

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Acknowledgements
This work was supported by grants from the National Science Foundation (BCS-1919892 and BCS-2142073) and William F. Milton Fund to R.N.C. and from the National Institute of Allergy and Infectious Disease (R00AI47165) to J.E.B.

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41579-023-00888-0.

Peer review information *Nature Reviews Microbiology* thanks Andrew Gewirtz, Emanuel Canfora and Yolanda Sanz for their contribution to the peer review of this work.