Curr Nutr Rep (2015) 4:340–347
DOI 10.1007/s13668-015-0146-2

DIABETES AND OBESITY (L QI, SECTION EDITOR)

Obesity, Diet and the Gut Microbiota

Anthony R. Bird[1] · **Michael A. Conlon**[1]

Published online: 12 October 2015

Abstract A possible causal role of the gut microbiota in human obesity is capturing interest. Recent experimental evidence and mechanistic hypotheses suggest that a 'dysbiotic' large bowel microbiota, induced mainly by poor diet, increases dietary energy bioavailability and storage in the host. However, research findings in both animals and humans are inconsistent and whether an altered gut microbiota meaningfully impacts host energetics remains an open question. Future intervention studies must control diet and other lifestyle factors that profoundly influence the composition and activity of the intestinal microbiota to define its potential role in and contribution to the human obesity problem.

Keywords Obesity · Gut · Microbiota · Microbiome · Diet · Lifestyle · Fibre · SCFA

Introduction

Obesity is a complex and refractory global public health issue that imposes a considerable economic burden on healthcare systems worldwide. Global prevalence has increased dramatically over the last few decades and now well over 1 billion people are overweight or obese [1].

Obesity is caused by a chronic, positive energy imbalance between energy consumption and energy expenditure resulting in the gradual accumulation of triglycerides mainly in adipose tissue. Genetics and multiple environmental exposures play a role but our understanding of the relative importance of the component factors that determine an individual's susceptibility to obesity is incomplete [2]. While the genetic basis is clearly important [3, 4], the rapid spread within and across populations points to the overwhelming importance of environmental factors. Modern (westernised) lifestyles are seen as major driving forces. Altered eating habits, the ready availability and affordability of energy-dense foods rich in fat and refined carbohydrates, combined with increasing sedentariness, are considered pivotal in the loss of energy homeostasis [5].

A less obvious environmental factor capturing the attention of researchers is the gut microbiota. Recent controlled studies, mostly in mice, provide causal evidence that large bowel microbes directly regulate energy metabolism of the host through a diversity of mechanisms and pathways [6–9]. While obesity and obesity-related chronic diseases have been linked to a colonic microbiota disrupted by poor lifestyle and choice of diet [10], there is as yet no consistent evidence that the gut microbiota per se makes a seminal contribution to excessive weight gain in humans.

In this paper, we briefly review the evidence for a role the large bowel microbiota might play in the development of human obesity. We also consider the driving influence of diet on that association and the possible consequences for energy homeostasis, weight gain and adiposity.

Human Gut Microbiota

The gut microbiota is often considered as a major organ in its own right given its large biomass, cellular density and diversity in taxa and function that impact human health [11]. Microbes colonise the gut (and other body surfaces) for our entire

This article is part of the Topical Collection on *Diabetes and Obesity*

✉ Anthony R. Bird
tony.bird@csiro.au

Michael A. Conlon
michael.conlon@csiro.au

[1] CSIRO Food & Nutrition, PO Box 10041, Adelaide BC, SA 5000, Australia

life. Nearly all are bacteria (and archaea), but viruses, yeasts and other fungi [12], as well as unicellular eukaryotes and helminths, are (or may be) present. Recent high throughput molecular techniques are revolutionising our understanding of the taxonomic composition and activities of gut microbes and their variation within and between individuals. Bacteria belonging to the Bacteroidetes and Firmicutes phyla predominate the faecal community (>90 %) [8]; another several phyla are usually present and many more are occasionally represented [13]. Common genera include *Bacteroides*, *Clostridium*, *Prevotella*, *Bifidobacterium*, *Lactobacillus*, *Escherichia*, *Ruminococcus* and *Streptococcus* [14]. Recent mapping of the faecal microbiota of Westerners indicates the presence of countless sub-species or strains [13, 15].

Large, inter-individual variation in composition is a defining feature of the intestinal microbial community. Each adult has a unique microbiota composition [13] that is comparatively stable in time but which is nevertheless responsive to environmental influences, particularly diet [16•, 17]. Composition at the dominant phyla level (Bacteroidetes/Firmicutes) is reasonably stable whereas abundances of marginal phyla are more volatile [14, 18]. Longitudinal studies of small cohorts of healthy adults reveal that the vast majority of strains change little with time [18] unlike relative abundances which fluctuate wildly. Despite considerable inter-individual variation in composition, molecular analyses have shown that there is commonality among microbial genes encoding proteins involved in house-keeping metabolic activities [13, 15]. Substantial overlap in functional capacity among microbial populations provides a fitness advantage to the microbiota.

Evidence has emerged that disturbance of taxonomic configurations of the gut microbiota (dysbiosis) possibly underpins development and/or progression of numerous non-communicable diseases and disorders, obesity included [7, 19–21]. A greater understanding of the factors that drive microbial population changes, and their physiological consequences, is crucial in determining the role of the intestinal microbiota in human health and disease.

Evidence Implicating the Gut Microbiota in the Genesis of Obesity

Animal Studies

Animal studies have been instrumental in advancing knowledge of a possible role of the gut microbiota in obesity. Large intestinal microbial communities of lean and obese rodents have been shown to differ in composition, the latter having a greater relative abundance of Firmicutes and proportionately lower abundance of Bacteroidetes [6, 7]. There is also greater representation of archaea [8] and proteobacteria [4] in obese animals as well as evidence of changes at lower phylogenetic levels (e.g. reductions in bifidobacteria).

Germ-free mice have little body fat, and colonising them with microbiota from mice raised conventionally (conventionalisation) results in rapid weight gain and an increase in adiposity [8, 9]. Fat deposition was also accelerated with cecal and faecal transplants from obese animal or human donors [3, 6, 22]. Germ-free mice were also considered resistant to diet-induced obesity. Studies in these and gnotobiotic models demonstrate that the acquisition of a gut microbiota stimulates adipose tissue accretion and that an obese phenotype is mediated by an 'obesogenic' microbiota [22, 23].

But, not all studies have produced comparable outcomes. Some have shown that germ-free mice gain weight at a similar rate to conventional mice, that they are also susceptible to diet-induced obesity and that the degree of protection depends on the type of (high-fat) diet that is fed or on the duration of feeding [24, 25]. Furthermore, an increase in the Firmicutes:Bacteroidetes ratio in response to a high-fat diet can occur in the absence of obesity [26]. Clearly, diet and other exogenous factors modulate the structure of the gut microbiota and, in turn, development of an obese phenotype. Indeed, the microbiota and associated phenotype are highly responsive to dietary perturbations [27].

Laboratory rodents are appropriate models because their gut microbiota is quantitatively different but qualitatively similar to that of humans [28]. Nevertheless, all models have limitations and extrapolation of research findings to free living humans can be problematic. Obesogenic rodent diets employ very high levels of fat, mostly saturated, to trigger excessive adiposity and weight gain in susceptible animals. By contrast, chow-fed controls have substantially lower weight gains. Rodents are commonly housed in cages with bedding, which is invariably eaten and, consequently, may produce unintentional changes in microbiota composition and metabolic activity [29••]. Rodents are coprophagic, and cohousing arrangements may consequently influence energy flux and gut microbial community dynamics [22] and study outcomes. Despite genetic similarity, even in outbred lines, only a proportion of animals in a given cohort are susceptible to diet-induced obesity despite being exposed to the same obesogenic environment as their lean counterparts [30]. The obese phenotype is diet-dependent, and hyperphagia may mediate greater weight gain observed in susceptible animals [31]. Differences in feed use efficiencies, energy metabolism and lipid accretion are common explanations for the greater accumulative weight gain of obesity-prone rodents [30]. However, an earlier study using isotopic tracer methodology offers a simpler explanation that obese animals simply eat more food [32].

Human Studies: Lean vs Obese

Complementary research in humans has produced results that were essentially parallel to those from animals. Numerous observational and descriptive studies have found overweight,

obesity and weight gain to be associated with pronounced compositional shifts in intestinal microbiota. A higher Firmicutes:Bacteroidetes ratio, which was observed in initial studies, is widely considered a hallmark of obesity [10, 33, 34]. But as with animal studies, results are mixed. Many failed to find a link between body mass index (BMI), or obesity, and relative abundances of the two main bacterial phyla [35, 36]. A lower bacterial richness and diversity was sometimes but not always [37] associated with greater adiposity and/or weight gain. Discordant results were also reported for indices at lower phylogenetic classifications. For instance, obesity has been linked to an increase in *Lactobacillus* spp. [33, 38] and a decrease in *Bifidobacterium* [33, 34].

Angelakis and colleagues [39] conducted a meta-analysis on obesity-associated components of the commensal flora and reported that the faecal *Bifidobacterium* population was smaller in obese compared to lean individuals in five of the six cohorts included in the analysis. Their analyses also revealed fewer Firmicutes and Methanobrevibacter, but no significant association was found for *Lactobacillus* or Bacteroidetes and obesity. These findings are based on several individual studies, albeit with reasonably large sample sizes, but the total number of studies in the analysis is still small. An even more recent meta-analysis of high throughput molecular sequencing studies was also unable to uncover distinct microbial signatures for obesity [40•]. An association between overweight and increased pathogenic bacterial load [34] is somewhat predictable but positive correlations between obesity (and overweight) and increases in bacteria normally considered conducive to host health, e.g. *Lactobacillus* [33, 38] and *Faecalibacterium prausnitzii* (a key butyrate producer with anti-inflammatory actions [41]), is less intuitive.

Weight reduction interventions have produced equally inconsistent outcomes. Increased proportions of *Lactobacillus* [34] and *Bacteroides* [42] have been associated with weight loss as has reduced numbers of *Bifidobacterium* [43, 44] and butyrate-producing bacteria (Firmicutes) [45]. The microbial response seems dependent on the nutrient composition of energy-reduced diets, particularly carbohydrate content [43, 45, 46]. According to Duncan et al. [42], weight loss itself neither drives nor is driven by associated changes in gut microbiota composition.

Factors Contributing to Gut Microbiota Compositional Variance

Aside from diet, there are myriad other factors that contribute to the large inter-individual variance in gut microbiota composition and, accordingly, potentially affect research outcomes and so could explain the lack of consistency among studies in compositional differences between lean and obese individuals. Study subject-related factors include age, gender, ethnicity/race, health status, frailty and living environment [47, 48].

Xenobiotics, including medications in addition to antibiotics, modulate microbiota composition [49]. Antibiotic use has long been associated with weight gain in humans and growth promotion in livestock. Emulsifiers commonly used in food manufacturing disrupt the gut microbiota-host relationship and possibly contribute to obesity [50]. Circadian disorganisation due to shift work, jet lag and sleep apnoea disrupts the large bowel microbiota [51•].

Obesity is a major cause of morbidity, reduced quality of life and disability [52]. Risk for serious ailments, including cardiometabolic diseases [53] and certain cancers [54], is increased greatly. Emergent evidence indicates that faecal phylogenetic diversity and composition correlate with disease onset and progression [55, 56]. Accordingly, accurate characterisation and monitoring of clinical phenotypes in observational and experimental studies is of crucial importance. Most studies though have deployed simple, inexpensive anthropometric markers of general (and abdominal) obesity which fail to discriminate between fat and lean mass. Furthermore, adipose tissue depots differ markedly in metabolic activity [57]. Their anatomical distribution (e.g. visceral and regional adiposity) is a major determinant of metabolic disease development and risk, and differences in BMI categorisation could contribute to inconsistent findings between studies.

Sample relevance and integrity are also important considerations in delineating intrinsic associations between gut microbiota and host health. For logistical reasons, stool samples from free-living study cohorts are commonly used. The faecal microbiota serves as a proxy for the distal luminal colonic microbial community. Taxonomic and biochemical composition of the intra-colonic environment varies depending on the anatomical site and ecological niche [14, 45, 58•]. Complete faecal collection, preferably over several days, rather than spot samples, is also an essential requirement given the inherent variation in faecal microbiology and biochemistry. Compliance by study participants with faecal collection, sampling and storage protocols (pre-DNA extraction) is vitally important for ensuring sample integrity and data precision.

Diet Shapes the Gut Microbiota

Amount and type of foods consumed have an overwhelming influence on the composition and function of the gut microbiota [16•]. Diet accounts for almost 60 % of the total variance in gut microbiota composition in animals [59, 60]. In humans, it is about 10 %, which is despite greater individual variation in genotype and other influences [44]. The strong influence of diet, and dietary components, on the microbiota is clearly evident in neonates and young children [18, 61]. Dietary milk non-digestible carbohydrates [62, 63] guide the ontogenic developmental trajectory of the infant gut microbiota, and those derived from breast milk augment infant gut microbial functional pathways [61] and composition [64]. Cessation of

breastfeeding, not the introduction of solid foods, appears to govern maturation of the microbiome [61], although increasing dietary nutrient diversity is associated with a concomitant expansion in microbial diversity and greater stability [18].

Dietary Patterns

Bacterial community structures generally reflect dietary patterns of the host. However, there have been few studies of dietary patterns (e.g. vegetarian, Mediterranean, western) within and across geographic regions, and the findings are somewhat contradictory. Generally, traditional, plant-based diets rich in non-digestible polysaccharides are associated with greater representation of Bacteroidetes [65, 66], which is not the case for western diets, which are typically high in fat and refined carbohydrates and low in dietary fibre, see [65, 67]. Dietary carbohydrates support greater abundance of *Bifidobacterium* and *Clostridium* clusters IV (*Ruminococcaceae*) and XIVa (*Lachnospiraceae*) [43, 68], but this depends on the type of carbohydrate [44].

Individual Foods and Dietary Constituents

The impact of diet, and to a larger degree individual dietary components, on the composition and activity of the gut microbiota remains poorly defined. The nature of the response has been shown to be dependent somewhat on baseline (pre-intervention) phylogenetic configuration [69] but faecal microbial diversity does not seem a reliable predictor [44]. The possibility of carryover effects of habitual and treatment diets [70] also needs careful consideration when designing clinical (and animal) studies.

Nutrients entering the large bowel ecosystem have a major bearing on microbiota form and function. Non-starch polysaccharides (NSP) account for 20 to 45 % of the dry matter supplied to the colon, monosaccharides and oligosaccharides a further 10 %, and starch and its partial hydrolysis products less than 10 % [71]. Most diets deliver small amounts of sugar alcohols and various low molecular weight carbohydrates, such as fructans, to the microbiota [72]. Certain carbohydrates, such as fructans and resistant starches, have profound stimulatory effects on large bowel microbiota activity [43, 46, 73]. While poorly fermented dietary fibres do not contribute directly to the chemical milieu of the gut lumen, they may provide a physical scaffold for resident and transitory microbes, thereby facilitating fermentation processes. Their presence also modulates intestinal motility, digesta transit and, accordingly, fermentation events.

Modern diets supply variable amounts of protein (5–15 g) and lipid (5–10 g) to the colon [67]. Whereas carbohydrates generally produce fermentation patterns that favour host health [74], dietary lipids and protein tend to have the opposite effect [75]. Amount and type of protein consumed have differential effects on the large bowel ecosystem and mucosal health [76–78]. A protein surplus relative to fermentable carbohydrate results in putrefactive fermentation and production of potentially toxic metabolites [74, 78]. The effect of dietary protein and fat on the gut microbiota has been reviewed recently [79].

A diversity of minor dietary-derived compounds found in plant foods impacts the gut microbiota, including polyphenols, lignin, carotenoids and tannins [80, 81]. Polyphenols are quantitatively the most important of these and although only small amounts (~1 g/day) enter the colon, they have a disproportionate influence on microbial population structures and metabolic activity [81, 82].

Diet does not Reliably Reflect Nutrient Supply to the Colonic Microbiota

Diet is an inaccurate gauge of substrate supply to the large bowel because numerous factors influence assimilation of foods in the upper gut. Many foods, especially those rich in dietary fibre, such as whole grains and brans, comprise a complex mix of non-digestible carbohydrates intimately associated with many different plant secondary compounds (co-passengers). The physical form modulates large bowel physiology and microbiota, and food components may act independently, additively and synergistically [83, 84]. Some dietary fibres for instance reduce small intestinal and whole tract digestibility of protein and fat [85]. Predicting interactions among dietary constituents is further complicated by processing, storage and preparation of component foods. Small intestinal functional capacity and digesta transit rate differ greatly between individuals, and some are far more efficient in digesting [86] and fermenting starch [44]. The capacity of the gut microbiota to utilise dietary fibre may be diminished in certain diseases, such as ulcerative colitis [87••].

Microbiota and Energy Harvest

Several interdependent mechanisms have been forwarded to explain the possible link between gut microbiota and obesity. Most are based on mechanistic evidence from animal studies, but there is limited evidence from human studies that a ‘dysbiotic’ microbiota is geared to convey more dietary energy to the host. Gordon and colleagues [9, 88] first conceived the intriguing notion that the microbiota of obese subjects has a greater propensity to extract more energy from the diet. The gut microbiota, no doubt, confers an evolutionary advantage to humans by salvaging dietary energy, mainly from dietary fibres, which would otherwise be inaccessible. Short chain fatty acids (SCFA) produced by colonic fermentation of carbohydrates (and protein) are absorbed by the bowel and supply the host with energy. SCFA also regulate food (energy)

intake and host metabolism through immune and neuroendocrine mechanisms [89].

That the microbiota increase energy flow to the host has been inferred mainly from increased SCFA levels and hydrolytic gene enrichment in microbiota of obese compared to lean subjects [6, 8, 9, 36, 88]. But, as with animal studies, increased SCFA levels did not always align with expected changes in major phyla abundances.

SCFA are minor energy sources for humans, supplying at most 10 % of energy requirements, although, for those consuming western diets, which are inherently low in fermentable carbohydrates, their contribution is likely to be only about 2 %. Luminal SCFA levels are highest in the proximal colon, the site of most active fermentation, and decline in an aborad direction. Because they are also rapidly absorbed by colonocytes, only ~5 % appear in faeces [90, 91]. Inter-individual differences in faecal SCFA concentrations are large and responses to dietary intervention highly variable [92]. Reported differences in faecal SCFA concentrations between lean, and overweight or obese, individuals are small (~20–30 %) [46, 93]. SCFA pools (total amount excreted in faeces or in digesta), perhaps a more informative metric in this context, were not reported. Quantitative information on SCFA flux is scarce and exceedingly difficult to acquire, especially in humans.

Reasons for the purportedly larger supply of dietary energy to the host are not apparent. Obese subjects need to eat more food to sustain a larger body mass and consequently more substrate would have reached the colon [94], presumably producing more SCFA. Upregulation of microbial saccharolytic capacity [6] is consistent with this scenario. Diet, and in particular the amount and type of fermentable fibres, is closely linked to gut microbial activity as reflected in faecal fermentation patterns and portal SCFA absorption [90].

Alternatively, an obesogenic (dysbiotic) microbiota might also be capable of fermenting a greater proportion of dietary fibre. About 75 % of fibre in mixed diets is fermented in the large intestine [91]. Further, energy gains could be achieved through greater fermentation efficiency. However, fibre consumption in most Western populations is low (<20 g/day for an adult [95]) and is a fraction of that consumed by ancestral populations [96]. Nevertheless, even a modest reduction in energy intake (~400 kJ/day) would help offset weight gain [97]. Whether such small improvements in energy balance would make meaningful inroads into combating the obesity problem though is a matter of debate.

Some of the established functions of SCFA, including their anorexigenic actions [98], argue against a role in dietary energy gain and so does the well-established role for dietary fibre in human health. A substantial body of evidence demonstrates that fibre is both preventative and therapeutic for major non-communicable diseases, including obesity and many of its comorbidities [99]. Animal studies show that dietary fibre consumption not only reduces food intake, weight gain and adiposity but it also improves indices of metabolic health [100, 101]. Nevertheless, the benefits of fibre may not be realised if the background diet is rich in fat [100, 101]. den Besten et al. [89] suggest that the beneficial actions of SCFA may be compromised in obese individuals or are insufficient to counter the detrimental effects of poor diet. Resistant starch fermentation is reduced, and its effects on adiposity diminished in rodents fed a high-fat diet [100]. Resistant starch fermentation is also impaired in obese but not lean mice [102], and higher dietary levels of this fibre may be necessary to reduce adiposity in obese phenotypes [103].

Conclusions

No signature faecal microbial profile of obesity has been found, and it is unclear if gut microbes are involved and how they might bring about weight gain and excessive adiposity. Human studies to date are sparse, mostly small scale and the findings are mixed. It is not yet known if microbial differences observed between lean and overweight or obese phenotypes are a cause or a consequence of human obesity.

Multiple exogenous factors influence intestinal microbiota composition and modulate the complex and dynamic interaction between it and its host. Diet is inextricably linked to both parties, and the age-old adage you are what you eat also certainly holds true for our gut microbiota. To understand whether the activity or content of the intestinal microbial community influences the energy economy of the host in a meaningful way will require well-designed randomized controlled trials using larger cohorts in which major confounding variables and interacting factors, especially diet, are better defined and tightly controlled.

Nonetheless, microbial ‘dysbiosis’, at least in the context of obesity, is essentially a manifestation of an unhealthy lifestyle, notably poor diet and possibly physical inactivity. It is also potentially an indicator of an individual’s risk of developing obesity-related health problems. But, regardless of whether the intestinal ecosystem abets adipose tissue accretion or not, the primary driver and overwhelming significance of poor lifestyle choices, and in particular excessive energy consumption, in the global obesity epidemic must be placed in perspective.

Compliance with Ethical Standards

Conflict of Interest Anthony R. Bird and Michael A. Conlon declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384:766–81.
2. Huang T, Hu FB. Gene-environment interactions and obesity: recent developments and future directions. Medical Genet. 2015;8 Suppl 1:S2–7.
3. Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R. Human genetics shape the gut microbiome. Cell. 2014;159:789–99.
4. Parks BW, Nam E, Org E, Kostem E, Norheim F, Hui ST, et al. Genetic control of obesity and gut microbiota composition in response to high-fat, high-sucrose diet in mice. Cell Metab. 2013;17:141–52.
5. Friedman JM. Causes and control of excess body fat. Nature. 2009;459:340–2.
6. Turnbaugh PJ, Backhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe. 2008;3:213–23.
7. Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci U S A. 2005;102:11070–5.
8. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444:1027–31.
9. Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A. 2004;101:15718–23.
10. Heinken A, Thiele I. Systems biology of host–microbe metabolomics. WIREs Syst Biol Med. 2015;7:195–219.
11. Burcelin R, Serino M, Chabo C, Garidou L, Pomie C, Courtney M, et al. Metagenome and metabolism: the tissue microbiota hypothesis. Diabetes Obes Metab. 2013;15 Suppl 3:61–70.
12. Romani L, Zelante T, Palmieri M, Napolioni V, Picciolini M, Velardi A. The cross-talk between opportunistic fungi and the mammalian host via microbiota's metabolism. Semin Immunopathol. 2015;37:163–71.
13. Huttenhower C, Gevers D, Knight R, Abubucker S, Badger JH, Chinwalla AT, et al. Structure, function and diversity of the healthy human microbiome. Nature. 2012;486:207–14.
14. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. Diversity of the human intestinal microbial flora. Science. 2005;308:1635–8.
15. Huse SM, Ye YZ, Zhou YJ, Fodor AA. A core human microbiome as viewed through 16S rRNA sequence clusters. PLoS One. 2012;7:e34242.
16. • David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505:559–63. **Intervention study showing the considerable capacity of the large bowel (fecal) microbiota to respond to dietary change.**
17. Simoes CD, Virtanen KA, Maukonen J, Scott KP, Pietilainen KH, Saarela M. Impact of a very low-energy diet on the fecal microbiota of obese individuals. Eur J Nutr. 2014;53:1421–9.
18. Voreades N, Kozil A, Weir TL. Diet and the development of the human intestinal microbiome. Front Microbiol. 2014;5:494.
19. Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. Gut. 2015;64(1):93–100.
20. Nielsen DS, Krych L, Buschard K, Hansen CHF, Hansen AK. Beyond genetics. Influence of dietary factors and gut microbiota on type 1 diabetes. FEBS Lett. 2015;588:4234–43.
21. Tai N, Wong FS, Wen L. The role of gut microbiota in the development of type 1, type 2 diabetes mellitus and obesity. Rev Endocr Metab Disord. 2015;16:55–65.
22. Ridaura VK, Jeremiah JF, Rey FE, Cheng J, Duncan AE, Kau AL, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341:1241214.
23. Fei N, Zhao L. An opportunistic pathogen isolated from the gut of an obese human causes obesity in germ free mice. ISME J. 2013;7:880–4.
24. Fleissner CK, Huebel N, Abd El-Bary MM, Loh G, Klaus S, Blaut M. Absence of intestinal microbiota does not protect mice from diet-induced obesity. Br J Nutr. 2010;104:919–29.
25. Zhao L. The gut microbiota and obesity: from correlation to causality. Nat Rev Microbiol. 2013;11:639–47.
26. Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, Keilbaugh SA, Hamady M, Chen Y-Y, et al. High-fat diet determines the composition of the murine gut microbiome independently of obesity. Gastroenterology. 2009;137:1716–24.
27. Zhang CH, Zhang MH, Pang XY, Zhao YF. Structural resilience of the gut microbiota in adult mice under high-fat dietary perturbations. ISME J. 2012;6:1848–57.
28. Krych L, Hansen CHF, Hansen AK, van den Berg FWJ, Nielsen DS. Quantitatively different, yet qualitatively alike: a meta-analysis of the mouse core gut microbiome with a view towards the human gut microbiome. PLoS One. 2013;8:e62578.
29. •• Le Leu RK, Conlon MA, Bird AR, Clarke JM. Housing experimental rats in solid-based cages with digestible bedding may confound outcomes of nutritional studies. J Sci Food Agric. 2015;95:2155–8. **Simple feeding trial demonstrating unequivocally that housing arrangements for experimental animals may compromise study outcomes.**
30. Hariri N, Thibault L. High-fat diet-induced obesity in animal models. Nutr Res Rev. 2010;23:270–99.
31. Buettner R, Scholmerich J, Bollheimer LC. High-fat diets: modeling the metabolic disorders of human obesity in rodents. Obesity. 2007;15:798–808.
32. Commerford SR, Pagliassotti MJ, Melby CL, Wei Y, Hill J. Inherent capacity for lipogenesis or dietary fat retention is not increased in obesity-prone rats. Am J Physiol Regul Integr Comp Physiol. 2001;280:R1680–7.
33. Million M, Angelakis E, Paul M, Armougom F, Leibovici L, Raoult D. Comparative meta-analysis of the effect of Lactobacillus species on weight gain in humans and animals. Microb Pathog. 2012;53:100–18.
34. Santacruz A, Collado MC, Garcıa-Valdes L, Segura MT, Martın-Lagos JA, Anjos T, et al. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. Br J Nutr. 2010;104:83–92.
35. Hu HJ, Park SJ, Jang HN, Choi MG, Park KH, Kang JH, et al. Obesity alters the microbial community profile in Korean adolescents. PLoS One. 2015;10:e0134333.
36. Schwiertz A, Taras D, Schafer K, Beijer S, Bos NA, Donus C, et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity. 2010;18:190–5.
37. Kasai C, Sugimoto K, Moritani I, Tanak J, Oya Y, Inoue H, et al. Comparison of the gut microbiota composition between obese and non-obese individuals in a Japanese population, as analysed by terminal restriction fragment length polymorphism and next-generation sequencing. BMC Gastroenterol. 2015;15:100–10.

38. Armougom F, Henry M, Vialettes B, Raccah D, Raoult D. Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and *methanogens* in anorexic patients. PLoS One. 2009;4:e7125.
39. Angelakis E, Armougom F, Amougom F, Million M, Raoult D. The relationship between gut microbiota and weight gain in humans. Future Microbiol. 2012;7:91–109.
40.• Walters WA, Xu Z, Knight R. Meta-analyses of human gut microbes associated with obesity and IBD. FEBS Lett. 2014;588: 4223–33. **Meta-analysis of a small number of studies that used comparable analytical methodologies. The analysis reveals that fecal microbiota differences between lean and obese are inconsistent across studies, indicative of a small effect size for obesity.**
41. Balamurugan R, George G, Kabeerdoss J, Hepsiba J, Chandragunasekaran AM, Ramakrishna BS. Quantitative differences in intestinal Faecalibacterium prausnitzii in obese Indian children. Br J Nutr. 2010;103:335–8.
42. Nadal I, Santacruz A, Marcos A, Warnberg J, Garagorri M, Moreno LA. Shifts in clostridia, bacteroides and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. Int J Obes. 2009;33:758–67.
43. Duncan SH, Belenguer A, Holtrop G, Johnstone AM, Flint HJ, Loblet GE. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. Appl Environ Microbiol. 2007;73: 1073–8.
44. Salonen A, Lahti L, Salojarvi J, Holtrop G, Korpela K, Duncan S. Impact of diet and individual variation on intestinal microbiota composition and fermentation products in obese men. ISME J. 2014;8:2218–30.
45. Duncan SH, Lobley GE, Holtrop G, Ince J, Johnstone AM, Louis P, et al. Human colonic microbiota associated with diet, obesity and weight loss. Int J Obes. 2008;32:1720–4.
46. Brinkworth GD, Noakes M, Clifton PM, Bird AR. Comparative effects of very low-carbohydrate, high-fat and high-carbohydrate, low-fat weight-loss diets on bowel habit and faecal short-chain fatty acids and bacterial populations. Br J Nutr. 2009;101:1493–502.
47. Prideaux L, Kang S, Wagner J, Buckley M, Mahar JE, De Cruz P, et al. Impact of ethnicity, geography, and disease on the microbiota in health and inflammatory bowel disease. Inflamm Bowel Dis. 2013;19:2906–18.
48. Dominianni C, Sinha R, Goedert JJ, Pei ZH, Yang LY, Hayes RB, et al. Sex, body mass index, and dietary fiber intake influence the human gut microbiome. PLoS One. 2015;10:e0124599.
49. Maurice CF, Haiser HJ, Turnbaugh PJ. Xenobiotics shape the physiology and gene expression of the active gut microbiome. Cell. 2013;152:39–50.
50. Cani PD, Everard A. Keeping gut lining at bay: impact of emulsifiers. Trends Endocrinol Metab. 2015;26:273–4.
51.• Thaiss CA, Zeevi D, Levy M, Zilverman-Shapira G, Suez J, Tengeler AC, et al. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. Cell. 2014;159: 514–29. **Comprehensive study in mice and humans showing that gut microbiota composition and function fluctuates largely in response to daily feeding rhythms, patterns and behaviours. Disrupted circadian rhythmicity impacts the microbiota (dysbiosis) which in turn may have adverse metabolic consequences for the host.**
52. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224–60.
53. Ebbert JO, Elrashidi MY, Jensen MD. Managing overweight and obesity in adults to reduce cardiovascular disease risk. Curr Atheroscler Rep. 2014;16:445.
54. Rogers CJ, Prabhu KS, Vijay-Kumar M. The microbiome and obesity—an established risk for certain types of cancer. Cancer J. 2014;20(3):176–80.
55. Kostic AD, Gevers D, Siljander H, Vatanen T, Hyotylainen T, Hamalainen A-M, et al. The dynamics of the human infant gut microbiome in development and in progression toward type 1 diabetes. Cell Host Microbe. 2015;17:260–73.
56. Zhang XY, Shen DQ, Fang ZW, Jie ZY, Qiu XM, Zhang CF, et al. Human gut microbiota changes reveal the progression of glucose intolerance. PLoS One. 2013;8(8):e71108.
57. Palmer BF, Clegg DJ. The sexual dimorphism of obesity. Mol Cell Endocinol. 2015;402:113–9.
58.• Ringel Y, Maharshak N, Ringel-Kulka T, Wolber EA, Sartor RB, Carroll IM. High throughput sequencing reveals distinct microbial populations within the mucosal and luminal niches in healthy individuals. Gut Microbes. 2015;6(3):173–81. **Observational study showing that the large bowel luminal (fecal) and mucosa-associated microbiota are essentially two distinct ecosystems that differ in microbial diversity and composition.**
59. Faith JJ, McNulty NP, Rey FE, McNulty NP, Rey FE, Gordon JI. Predicting a human gut microbiota's response to diet in gnotobiotic mice. Science. 2011;333:101–4.
60. Zhang CH, Zhang MH, Wang SY, Han RJ, Cao YF, Hua WY. Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. ISME J. 2010;4(2):232–41.
61. Backhed F, Roswall J, Peng YQ, Feng Q, Jia HJ, Kovatcheva-Datchary P, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe. 2015;17(5):690–703.
62. Pacheco AR, Barile D, Underwood MA, Mills DA. The impact of the milk glycobiome on the neonate gut microbiota. Annu Rev Anim Biosci. 2015;3:419–45.
63. Jost T, Lacroix C, Braegger C, Chassard C. Impact of human milk bacteria and oligosaccharides on neonatal gut microbiota establishment and gut health. Nutr Rev. 2015;7 3(7):426–37.
64. Wang M, Li M, Wu S, Lebrilla CB, Chapkin RS, Ivanov I, et al. Fecal microbiota composition of breast-fed infants is correlated with human milk oligosaccharides consumed. J Pediatr Gastroenterol Nutr. 2015;60(6):825–33.
65. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen Y-Y, Keilbaugh SA, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011;334:105–8.
66. Bervoets L, Van Hoorenbeeck K, Kortleven I, Van Noten C, Hens N, Vael C. Differences in gut microbiota composition between obese and lean children: a cross-sectional study. Gut Pathog. 2013;5:10.
67. Conlon MA, Bird AR. The impact of diet and lifestyle on gut microbiota and human health. Nutrients. 2015;7(1):17–44.
68. Walker AW, Ince J, Duncan SH, Webster LM, Holtrop G, Ze XL. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. ISME J. 2011;5(2):220–30.
69. Korpela K, Flint HJ, Johnstone AM, Lappi J, Poutanen K, Dewulf E. Gut microbiota signatures predict host and microbiota responses to dietary interventions in obese individuals. PLoS One. 2014;9(3):e90702.
70. Le Leu RK, Winter JM, Christophersen C, Young GP, Humphreys KJ, Hu Y, et al. Butyrylated starch intake can prevent red meat induced O6-methyl-2-deoxyguanosine adducts in human rectal tissue: a randomised clinical trial. Br J Nutr. 2015;114(2):220–30.
71. Bird AR, Usher S, May B, Topping DL, Morell MK. 2012. Resistant starch—measurement, intakes and dietary targets. In: Dietary Fiber and Health. Eds Susan Cho and Nelson Almeida. pp 41–56.

72. Payne AN, Chassard C, Lacroix C. Gut microbial adaptation to dietary consumption of fructose, artificial sweeteners and sugar alcohols: implications for host-microbe interactions contributing to obesity. Obes Rev. 2012;13(9):799–809.
73. Gibson GR, Probert HM, Van Loo J, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. Nutr Res Rev. 2004;17(2):259–75.
74. Russell WR, Gratz SW, Duncan SH, Holtrop G, Ince J, Scobbie L, et al. High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. Am J Clin Nutr. 2011;93(5):1062–72.
75. Silvester KR, Bingham SA, Pollock JRA, Cummings JH, ONeill IK. Effect of meat and resistant starch on fecal excretion of apparent N-nitroso compounds and ammonia from the human large bowel. Nutr Cancer. 1997;29(1):13–23.
76. O'Callaghan NJ, Toden S, Bird AR, Topping DL, Fenech M, Conlon MA. Colonocyte telomere shortening is greater with dietary red meat than white meat and is attenuated by resistant starch. Clin Nutr. 2012;31:60–4.
77. Winter J, Nyskohus L, Young GP, Hu Y, Conlon MA, Bird AR, et al. Inhibition by resistant starch of red meat-induced promutagenic adducts in mouse colon. Cancer Prev Res. 2011;4:1920–8.
78. Toden S, Bird AR, Topping DL, Conlon MA. Differential effects of dietary whey, casein and soya on colonic DNA damage and large bowel SCFA in rats fed diets low and high in resistant starch. Br J Nutr. 2007;97:535–43.
79. Maukonen J, Saarela M. Human gut microbiota: does diet matter? Proc Nutr Soc. 2015;74:23–36.
80. Belobrajdic DP, Bird AR. The potential role of phytochemicals in wholegrain cereals for the prevention of type-2 diabetes. Nutr J. 2013;12:62.
81. Tuohy KM, Conterno L, Gasperotti M, Viola R. Up-regulating the human intestinal microbiome using whole plant foods, polyphenols, and/or fiber. J Agric Food Chem. 2012;60(36):8776–82.
82. Martin FPJ, Montoliu I, Nagy K, Moco S, Collino S, Guy P. Specific dietary preferences are linked to differing gut microbial metabolic activity in response to dark chocolate intake. J Proteome Res. 2012;11(12):6252–63.
83. Muir JG, Yeow EGW, Keogh J, Pizzey C, Bird AR, Sharpe K, et al. Combining wheat bran with resistant starch raised faecal butyrate and lowered phenols in humans. Am J Clin Nutr. 2004;79:1020–8.
84. Bird AR, Vuaran M, Crittenden R, Hayakawa T, Playne M, Brown I, et al. Comparative effects of a high-amylose starch and a fructooligosaccharide on fecal bifidobacteria numbers and short-chain fatty acids in pigs fed *Bifidobacterium animalis*. Dig Dis Sci. 2009;54(5):947–54.
85. Baer DJ, Rumpler WV, Miles CW, Fahey GC. Dietary fiber decreases the metabolizable energy content and nutrient digestibility of mixed diets fed to humans. J Nutr. 1997;127(4):579–86.
86. Thornton JR, Dryden A, Kelleher J, Losowsky MS. Super-efficient starch absorption—a risk factor for colonic neoplasia. Dig Dis Sci. 1987;32(10):1088–91.
87.•• James SL, Christophersen CT, Bird AR, Rosella O, Muir JG, Gibson PR. Abnormal fibre usage in UC in remission. Gut. 2015;64(4):562–70. **Randomised controlled trial showing that the gut microbiota of patients with quiescent ulcerative colitis has a reduced capacity to ferment dietary fibres such as resistant starch and nonstarch polysaccharides.**
88. Backhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science. 2005;307:1915–20.
89. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud D-J, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013;54:2325–40.
90. Bach Knudsen KE. Microbial degradation of whole-grain complex carbohydrates and impact on short-chain fatty acids and health. Adv Nutr. 2015;6:206–13.
91. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev. 2001;81:1031–64.
92. McOrist AL, Miller RB, Bird AR, Keogh JB, Noakes M, Topping DL, et al. Fecal butyrate levels vary widely among individuals but are usually increased by a diet high in resistant starch. J Nutr. 2011;141:883–9.
93. Rahat-Rozenbloom S, Fernandes J, Gloor GB, Wolever TMS. Evidence for greater production of colonic short-chain fatty acids in overweight than lean humans. Int J Obes. 2014;38(12):1525–31.
94. Cox LM, Blaser MJ. Pathways in microbe-induced obesity. Cell Metab. 2013;17(6):883–94.
95. Hooper B, Spiro A, Stanner S. 30 g of fibre a day: an achievable recommendation? Nutr Bull. 2015;40:118–29.
96. Leach JD. Evolutionary perspective on dietary intake of fibre and colorectal cancer. Eur J Clin Nutr. 2007;61:140–2.
97. Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and environment: where do we go from here? Science. 2003;299:854–5.
98. Graham C, Mullen A, Whelan K. Obesity and the gastrointestinal microbiota: a review of associations and mechanisms. Nutr Rev. 2015;73(6):376–85.
99. Yang Y, Zhao L-G, Wu Q-J, Ma X, Xiang Y-B. Association between dietary fibre and lower risk of all-cause mortality: a meta-analysis of cohort studies. Am J Epidemiol. 2015;181(2):83–91.
100. Higgins JA. Resistant starch and energy balance: impact on weight loss and maintenance. Crit Rev Food Sci Nutr. 2014;54:1158–66.
101. Keenan MJ, Zhou J, Hegsted M, Pelkman C, Durham HA, Coulon DB, et al. Role of resistant starch in improving gut health, adiposity, and insulin resistance. Adv Nutr. 2015;6:198–205.
102. Zhou J, Martin RJ, Tulley RT, Raggio AM, Shen L, Lissy E, et al. Failure to ferment dietary resistant starch in specific mouse models of obesity results in no body fat loss. J Agric Food Chem. 2009;57(19):8844–51.
103. Belobrajdic DP, King RS, Christophersen CT, Bird AR. Dietary resistant starch dose-dependently reduces adiposity in obesity-prone and obesity–resistant male rats. Nutr Metab. 2012;9:93.