

# Fat and skinny bacteria?

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## INTRODUCTION

Due to the increased availability of high-throughput DNA-sequencing technologies and quantitative PCR, investigators have flooded the scientific literature with reports describing the composition of different gastrointestinal microbiotas. With the use of gnotobiotic isolators housing axenic animals, i.e. germ- or microbiota-free animals, investigators have also undertaken more hypothesis-driven research addressing putative roles for the microbiota in host health. Possibly inspired by the patent spread and pathogenesis of obesity and metabolic syndrome, in combination with the observation that a commonly used strain of germ-free laboratory mice are more resistant to obesity than their conventional counterparts,<sup>1</sup> a major focus of much of this work has considered the relationship between the microbiota of the host and the susceptibility of the host to obesity. Additionally, compared to many existing and theoretic therapeutics to counter the obesity pandemic, the microbiota is potentially a more practical target. I attempt to very briefly summarize, for nonprofessionals of microbiome study, the composition of the microbiota as it relates to obesity in humans. This is intended to provide the reader with sources for finding further information, including primary research that has contributed to our knowledge and more comprehensive reviews on the relevant topics mentioned.

## COMPOSITION OF THE OBESE MICROBIOTA

### Rejecting the *Bacteroidetes*: *Firmicutes* ratio

Bacterial 16S DNA sequencing of stool samples from obese and non-obese individuals has revealed significant differences in their respective microbiotas.<sup>2-7</sup> Indeed, the microbiota isolated from obese individuals is commonly designated as “dysbiotic,” a term meaning microbial imbalance or abnormal microbiota. However, how the microbiota is abnormal is not at all well understood, largely because what makes a healthy microbiota is not well understood. A frequently reported measure describing the microbiota is the ratio of *Bacteroidetes* to *Firmicutes*, two phyla that represent the most

abundant bacterial species in human stool.<sup>8,9</sup> More often, a decreased ratio—where *Bacteroidetes* are under-represented and *Firmicutes* are over-represented—is reported in obesity compared to healthy-weight controls,<sup>6,10-12</sup> yet some reports have identified an increased ratio of *Bacteroidetes* to *Firmicutes*.<sup>5,13</sup> Still others have reported an increase in the abundance of both phyla in the microbiota of obese individuals,<sup>14</sup> while additional studies have found no association between the abundance of *Bacteroidetes* nor *Firmicutes* in the microbiotas of obese and healthy-weight individuals.<sup>4,9,15</sup> Thus, the actual significance of the relative abundance of the two phyla, which are composed of thousands of distinct bacterial species, is extremely controversial. For a more comprehensive review of the members of *Bacteroidetes* and their connections to obesity, see Johnson et al.<sup>16</sup>

### Diversity is not created equally

Most commonly, and perhaps less controversially, the microbiota of obese individuals is described as having reduced bacterial diversity. Of course, how diversity is calculated and reported is not entirely consistent, but certain trends have emerged, particularly the obese microbiota exhibiting reduced richness, a measure of  $\alpha$ -diversity (within a single sample) which signifies the number of unique microbial species.<sup>4,7</sup> For instance, in a fairly large study of nearly 600 American adults, Peters et al observed that the richness of the microbiota of obese individuals was significantly reduced compared to that of overweight (but not obese) and healthy-weight participants. However, when accounting for the evenness of the microbial populations within each sample, differences in  $\alpha$ -diversity failed to reach significance.<sup>4</sup> Another fairly large study of approximately 300 Danish individuals found that the sampled microbiotas demonstrated a bimodal distribution with regard to richness.<sup>7</sup> Significantly more individuals in the group with lower microbial richness were obese and showed increased markers of metabolic syndrome, e.g. increased serum leptin, triglycerides, and hyperinsulinemia. Furthermore, in both this and an accompanying study,<sup>17</sup> microbial genes for metabolic pathways associated with inflammatory stress and production of potentially

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deleterious metabolites were proportionally increased in the microbiomes with decreased richness. Interestingly though, when comparing the microbiomes of obese and non-obese individuals, fewer differences were identified than when the groups were divided based on microbial richness.<sup>7</sup>

Other metrics that can be incorporated into measures of diversity, arguably more valuable than richness or evenness alone, include microbial phylogeny<sup>18</sup> and function.<sup>19</sup> Phylogenetic diversity takes into account the degree of evolutionary relatedness of the resident microbiota. Several studies already mentioned account for microbial phylogeny when determining the diversity of the population.<sup>3,6-9,20</sup> Importantly, increased diversity, as measured by 16S DNA, does not simply signify a “healthy microbiota”. Functional diversity, on the other hand, considers the entire microbial genome, the microbial transcriptome, proteome and/or other microbial-derived metabolites, i.e. the functional collective of the entire microbiome. Significant findings concerning the basic behavioral interactions between members of the microbiota, e.g. reinforcing microbiota stability through microbial interactions, are based on transcriptome or metabolome profiles.<sup>21-23</sup> It is fairly intuitive to appreciate how increased functional diversity may represent a healthier gut ecosystem. For example, functional diversity and redundancy may enable better adaptation to changes in physiology,<sup>24,25</sup> diet,<sup>9,26</sup> or exposures to medication.<sup>27</sup> Indeed, even though a small study of 25-32 year old twin pairs and their mothers revealed the gut microbiotas of obese individuals were more similar to each other than the similarity of microbiotas of lean participants to each other, no apparent overlap of phylotypes amongst microbial samples emerged. Instead, distinct functional cores, representing key metabolic pathways, emerged between the microbiomes of obese individuals compared to non-obese individuals.<sup>3</sup>

### “Specie-fic” differences that are real and reproducible?

So far the distinction between the microbiota compositions of the obese compared to the non-obese is a matter of reduced number, evenness, relatedness, and/or function of the resident species. Summarizing the relevance of specific microbial differences is complicated by the finding that microbial community variations between studies tend to be much greater than between obese and non-obese groups within studies.<sup>28,29</sup> In addition, sampling biases and insufficient sequencing depths impact how well microbial samples accurately represent their true ecosystems, and rarefaction performed in

order to make comparisons across studies further impacts the accuracy of sampled data. One potentially more conserved gut microbial phenotype correlated with individuals who are obese or have low microbial richness is increased abundance of the less dominant phylum *Proteobacteria*.<sup>4,7,20</sup> Although not a specific observation, members of several comprising genera, e.g. *Escherichia* and *Salmonella*, represent potential human pathogens.<sup>30</sup> This is potentially relevant because obesity is also associated with increased inflammation; thus, many have investigated the role of the microbiota in obesity-related inflammation (reviewed by McPhee and Schertzer).<sup>31</sup> Alternatively, Dao et al found that increased or high abundance of *Akkermansia muciniphila* (in addition to overall microbial richness) in overweight and obese subjects after six weeks on a calorie restricted diet was associated with improved metabolic profiles.<sup>32</sup> Importantly, *A. muciniphila* has been identified by several investigators as a species capable of conferring protection against obesity and metabolic disorders in animals,<sup>33-36</sup> so the case for an effective probiotic is arguably best-made in support of *A. muciniphila*.<sup>37</sup> Despite the paucity of more specific, reproducible microbial associations with the obese phenotype, some studies have demonstrated that obese and lean human fecal microbiotas can transfer those phenotypes to animals,<sup>38-40</sup> demonstrating that perhaps a variety of microbiota compositions may impact susceptibility to obesity. Additional research with animal models has provided significantly more insight into the composition and role of the gut microbiota in obesity and metabolic syndrome, as well as revealed possible mechanisms supporting their relationship,<sup>1,6,41-47</sup> but how well the results from animal studies reflect the gut microbiota and obesity in humans is still unknown.

## CONCLUSION

In spite of the large amount of available data describing microbial associations with human obesity, microbial-related mechanisms that impact host metabolism, and the transmissibility of obesity, especially in animal-to-animal models, there are no clear obesogenic microbiota phenotypes. Indeed, few compositional characteristics of the obese microbiotas considered herein appeared to be conserved across different studies, with the possible exception of some measure of reduced diversity compared to the non-obese microbiotas. It seems as though future work may unravel distinct, organism-independent, microbial functions that, when combined with certain dietary inputs or physiological aspects of the host, may enhance

susceptibility to obesity. Beyond the scope of this commentary, but critical to the understanding of a putatively obesogenic microbiota, is the irrefutable role of diet on the composition and metabolism of the microbiota, as well as on the metabolism of the host (reviewed by Sonnenburg and Backhed).<sup>48</sup> Naturally, what we feed ourselves directly impacts what we feed our microbiota, and the functional metabolic pathways expressed by the resident microbiota will influence which organisms can flourish with those dietary inputs and what microbiota-derived metabolites are produced. Future work describing the compositional and functional variation that is possible across different healthy microbiotas, as well as compositional and/or functional similarities conserved across different healthy microbiotas, should provide a better platform for investigating, and eventually understanding, the abnormal character of a “dysbiotic” microbiota, as it relates to any human pathology.

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