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News & views

Medical research

Statin drugs might boost healthy gut microbes

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An analysis of faecal samples reveals that obese people who take cholesterol-lowering statin drugs have a 'healthier' community of gut microorganisms than would be expected. What are the implications of this surprising finding?

Our digestive systems harbour more bacterial cells than there are human cells in our bodies. Although the often-mentioned estimate of a tenfold excess of microorganisms over human cells might exaggerate the ratio[1], even conservative estimates[2] accord the microbes numerical dominance at a ratio of about 1.3:1. These close gut microbial neighbours of ours comprise around 0.3% of a person's mass[2], and there are more than 100 times more bacterial genes in the gut[3] than there are genes in their human host. Interest has burgeoned in the potential effects of these normal gut residents (sometimes termed commensal bacteria) on our well-being. Writing in *Nature*, Vieira-Silva *et al.*[4] report an unexpected discovery, regarding patterns of gut microbes, that might have clinical consequences.

When trying to assess the daunting complexity of the many thousands of bacterial species in our gut, one option available is a categorization method[5] that assigns an individual's microbial profile to one of four groupings called enterotypes (Fig. 1), depending on the abundance of signature species. Those of us not immersed in the world of bacterial binomials owe a debt of gratitude to the colonically oriented colleagues who came up with this and other possible classification approaches.

The 'dysbiotic' enterotype called *Bacteroides* 2 (Bact2) is associated with inflammation[6]. People who have this enterotype tend to have a lower load of gut microbes than do those with other enterotypes, and more *Bacteroides* bacteria than *Faecalibacterium* microbes. These individuals also have a higher blood concentration of C-reactive protein — a hallmark of inflammation — than do individuals who have other enterotypes[7].

A cascade of data from the colonic cognoscenti links the composition of gut microbes to aspects of health. For example, more than 75% of individuals who have inflammatory bowel disease have the Bact2 enterotype, whereas fewer than 15% of people who do not have the disease harbour this enterotype[6]. Beyond the gut, many researchers have implicated gut microbes in obesity[8] and the cluster of conditions referred to as metabolic syndrome. However, the nature of the relationship between microbes and these conditions remains under debate.

Studies have also linked gut bacteria to cardiovascular disease. Molecules such as trimethylamine oxide, which are made by gut bacteria, might accelerate atherosclerosis, and their presence is associated with adverse cardiovascular outcomes, including death[9]. Vieira-Silva *et al.* report that the Bact2 mix of intestinal bacteria is characterized by a paucity of bacterial producers of another microbial molecule, butyrate. This short-chain fatty acid might help to preserve the barrier function of the epithelial cells that line the gut, perhaps preventing leakage of harmful bacterial endotoxin molecules from the bowel and thereby dampening systemic inflammation of the body[10].

In their quest for a potential connection between the bacterial population of the gut and obesity, Vieira-Silva and colleagues made a striking discovery when they mined data collected in a European Union study called the MetaCardis project (http://www.metacardis.net). This project has gathered data on the composition of human gut microbes using state-of-the-art technology, to assess the microbes' role in cardiovascular disease. More than 2,000 individuals recruited from European countries took part in an exhaustive survey that collected data for around 1,400 variables, such as medication taken and body-mass index (a measure used to assess a person's weight that takes height into account).

Vieira-Silva *et al.* report that in a subset

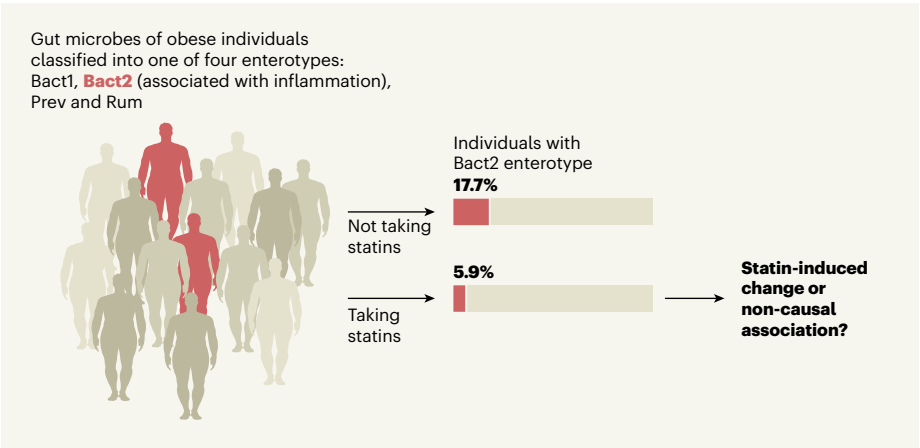

Figure 1 | Gut-microbe changes associated with the use of statin drugs. A person's gut microorganisms can be classified[5], by the analysis of faecal samples, into one of four groups called enterotypes, depending on the abundance of particular microbial species. These groupings are termed *Bacteroides* 1 (Bact1), *Bacteroides* 2 (Bact2), Ruminococcaceae (Rum) and *Prevotella* (Prev). The Bact2 enterotype is associated with health problems and inflammation[6]. Vieira-Silva *et al.*[4] assessed enterotype data for individuals who were recruited as part of a project to understand factors influencing cardiovascular health. The authors made the unexpected discovery that the prevalence of the Bact2 enterotype was lower than expected in obese individuals who were taking cholesterol-lowering drugs called statins. Whether this decrease in prevalence of the Bact2 enterotype in obese individuals is directly caused by statins or is due to another factor associated with statin use (if individuals taking statins have better access to health care, for example) will require further study.

of nearly 900 participants whose data they analysed, a higher prevalence of the Bact2 enterotype correlated with a higher body-mass index and obesity. However, the authors made the striking discovery that the pattern of enterotypes found in the population of obese individuals differed significantly depending on whether people were taking cholesterol-lowering drugs called statins (comprising about 12% of those studied). This result raised a surprising possible connection between statin intake and gut microbes. The obese participants taking statins had a significantly lower prevalence of the Bact2 enterotype (5.9% of the obese population) than did their obese counterparts not taking statins (17.7% of the obese population). Vieira-Silva and colleagues confirmed this phenomenon in an independent data set from the Flemish Gut Flora Project[11].

The use of statins is one of the great success stories of modern cardiovascular therapeutics. Originally derived from natural products of microbial denizens of the soil, these agents inhibit a rate-limiting enzyme in the pathway that makes cholesterol. By lowering cholesterol production, the treatment coaxes cells to boost the expression of receptors for low-density lipoprotein (LDL) that capture cholesterol-rich LDL particles, and this results in a robust decrease in cholesterol in the bloodstream. This LDL reduction substantially lowers the risk of cardiovascular events such as heart attack and stroke in a large swathe of the population at risk of such conditions, and many people use drugs of the statin class. Large meta-analyses of the effects of statin treatment reveal that it prolongs lifespan and that, on balance, the benefits outweigh any unwanted effects[12].

Independently of their effects on LDL, statins have anti-inflammatory actions that probably contribute to their clinical benefit through well-established molecular mechanisms[13]. However, no statin study has singled out obese individuals as targets for therapy, and no current guideline recommends considering obesity when making decisions about using statins for treatment.

Vieira-Silva and co-workers' unexpected findings therefore raise intriguing questions relating to the clinical use of statins. Yet interpretation of these findings warrants caution, in particular with regard to the risk of confusing correlation with causation. As the authors of this large and carefully executed study rightfully acknowledge, we should consider whether statin takers have had better access to health care or been more engaged in other health-promoting behaviours than have the individuals who were not taking statins. A large-scale clinical trial to determine whether statins lead to a reduced prevalence of the Bact2 enterotype in obese participants who would not otherwise receive statins could address this possibility, which is known as confounding by indication. Moreover, whether these findings apply across ethnic groups will require further study. In any case, following up on these provocative observations promises to provide new mechanistic insight into the complex relationships between obesity, metabolic status, gut microbes and cardiovascular disease.

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