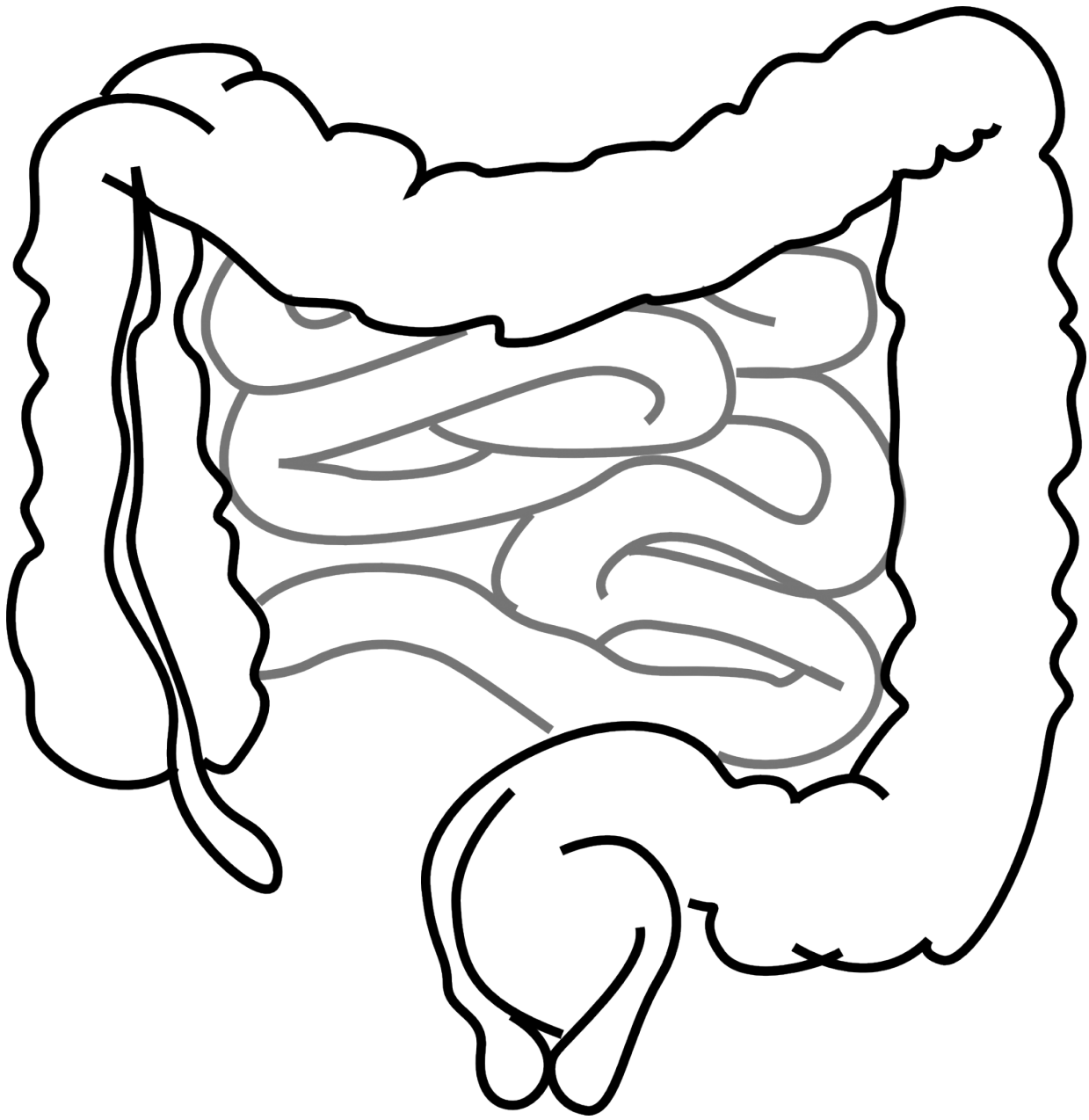
Obesity is linked to gut microbiota disturbance, but not among statin-treated individuals

May 6 2020



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In 2012, the European Union MetaCardis consortium, comprising 14 research groups from six European countries with multidisciplinary expertise set out to investigate a potential role of the gut microbiota in

the development of cardio-metabolic diseases. This project, coordinated by Prof Karine Clément at INSERM (France) studies more than 2,000 deeply phenotyped European participants in health and at different stages of cardiometabolic disease (obesity, diabetes and cardiovascular diseases).

Today, research teams led by Jeroen Raes (VIB-KU Leuven) and Prof. Clément (INSERM, Paris), together with the Metacardis consortium, publish their first findings in the authoritative journal *Nature*, identifying the common cholesterol-lowering drug statins as a potential microbiota-modulating therapeutic.

In their manuscript entitled "Statin therapy associates with lower prevalence of gut microbiota dysbiosis," Jeroen Raes (VIB-KU Leuven) and colleagues explore gut bacteria in a Metacardis cohort subset comprising nearly 900 individuals from three countries (France, Denmark and Germany) with BMI ranging between 18 and 73 kg.m-2. While the intestinal microbiota in obese individuals had previously been shown to differ from those in lean subjects, the unique experience of the Raes Lab in quantitative microbiome profiling allowed the researchers to shed a whole new light on microbiota alterations associated with obesity.

Prof. Jeroen Raes says, "Recently, our lab identified a single gut microbiota configuration (enterotype) with increased prevalence among patients suffering from intestinal inflammation (inflammatory bowel disease), multiple sclerosis, and depression. We observed this disturbed enterotype to be characterized by low bacterial abundances and biodiversity, notably deficient in some anti-inflammatory bacteria such as Faecalibacterium. In fact, even among healthy individuals, we detected slightly higher inflammation levels in carriers of what we refer to as the Bacteroides2 (Bact2) enterotype. As obesity is known to result in increased systemic inflammation levels, we hypothesized that Bact2 would also be more prevalent among obese study participants."

Exploring gut microbiota configurations of lean and obese volunteers, the MetaCardis researchers observed that Bact2 prevalence increased with BMI. While only 4% of lean and overweight subjects were characterized as Bact2 carriers, percentages sharply rose to 19% among obese volunteers. The same trend was observed among 2,350 participants of the VIB-KU Leuven Flemish Gut Flora Project population cohort.

Sara Vieira-Silva (principal author, VIB-KU Leuven): "We found systemic inflammation in participants carrying the Bact2 enterotype to be higher than expected based on their BMI. Even though this study design does not allow inferring causality, our analyses do suggest that gut bacteria play a role in the process of developing obesity-associated comorbidities by sustaining inflammation. While these key findings confirmed our study hypothesis, the results we obtained when comparing statin-treated and -untreated participants came as a total surprise."

Statins are commonly prescribed to reduce risk of developing cardio-metabolic diseases. Besides their target cholesterol-lowering effects, statins also tend to appease patients' systemic inflammation levels. Now, Vieira-Silva and colleagues have identified an additional potential beneficial effect of statin therapy on the gut microbiota. In obese individuals, the prevalence of the dysbiotic Bact2 enterotype was significantly lower in those taking statins (6%) than in their non-treated counterparts (19%) - comparable to levels observed in non-obese participants (4%). These striking observations were validated not only in the independent Flemish Gut Flora Project dataset, but also in an additional MetaCardis subset consisting of 280 patients with cardiovascular diseases.

Sara Vieira-Silva says, "These results suggest statins could potentially modulate the harmful gut microbiota alterations sustaining inflammation in obesity. Several interpretations of our results remain possible. On one

hand, by appeasing gut inflammation, statin therapy might contribute to a less hostile gut environment, allowing the development of a healthy microbiota. On the other hand, a direct impact of statins on bacterial growth has been previously demonstrated, which could possibly benefit non-inflammatory bacteria and underlie anti-inflammatory effects of statin therapy."

For many years, microbiota modulation strategies have been revolving around dietary interventions, (next-generation) pro- and prebiotics, introducing or promoting growth of beneficial bacteria. Only recently, a revived interest in the effect of small molecules and drugs on the colon ecosystem appeared. This study will further fuel that momentum.

Prof. Jeroen Raes says, "The potential beneficial impact of statins on the gut microbiota opens novel perspectives in disease treatment, especially given the fact that we have associated the Bact2 enterotype with several pathologies in which a role of the gut microbiota has been postulated. Our results open a whole range of possibilities for novel, gut microbiota modulating drug development."

At the same time, the MetaCardis team insists on a careful interpretation of their study results.

While promising, the findings reported are based on cross-sectional analyses, as opposed to following a treatment timeline. This means causality cannot be claimed based on these observations, nor can the researchers exclude that unaccounted factors could have played a role. For example, statin-medicated participants might have adopted a radically healthy lifestyle after being diagnosed with an increased risk of developing cardio-metabolic disease, which could have had a profound impact on their gut ecosystem.

"Thus," the researchers warn, "while our results are definitely promising,

they require further evaluation in a prospective clinical trial to ascertain whether the effect is reproducible in a randomized population, before considering the application of statins as microbiota-modulating therapeutics."

The present study is part of a greater effort in unraveling the role of the gut microbiota in cardiovascular disease by the European Commission-sponsored MetaCardis consortium.

Prof. Karine Clément, principal investigator of the clinical Metacardis cohort, says, "As a key risk factor in heart disease, part of consortium research efforts was dedicated to sketching up a comprehensive blueprint of gut microbiota alterations associated with obesity. More is to come: MetaCardis is also exploring if and which microbiota disturbances could, beyond obesity, further contribute to the progression of cardio-metabolic pathologies. The ultimate goal of our research is to unravel the role of gut bacteria in the development of heart diseases and, on the longer term, to be able to propose innovative diagnostic, preventive, and even therapeutic tools based on novel microbiota insights. The consortium is currently wrapping up multiple additional studies, so stay tuned!"

More information: Statin therapy is associated with lower prevalence of gut microbiota dysbiosis, *Nature* (2020). DOI: 10.1038/s41586-020-2269-x , www.nature.com/articles/s41586-020-2269-x

Provided by VIB (the Flanders Institute for Biotechnology)

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