Dietary fat and the faecal microbiome: where collinearity may lead to incorrect attribution of effects to fat

We read with interest the study reported by Yi Wan and colleagues, who examined the relative effects of high-fat and low-fat diets on the gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors.[1] The authors should be congratulated for the remarkable achievement of performing a feeding study on 217 young adults for 6 months with impressive retention rate. They concluded that higher fat consumption was associated with unfavourable changes in gut microbiota, faecal metabolomic profiles and systemic inflammation, and implied that difference in dietary fat was causally related to the changes observed, as evidenced by the title of the paper. While the study has been beautifully performed, we believe that the results have been misinterpreted.

The authors have overlooked the importance of the associated alterations in non-digestible carbohydrates. The intake of dietary fibre, as defined by a food content database, was maintained at the very low baseline level of consumption, estimated to be around 14 g/day across all diets. However, by virtue of the need to increase carbohydrate intake to 60% of macronutrients in the low-fat diet compared with 40% for the high-fat diet, the intake of two non-digestible carbohydrates not included in the database was increased. First, resistant starch is present in 3% of white rice and 2% of wheat flour (bread). Second, wheat flour is also a rich source of oligosaccharide fermentable oligo-,di-,mono-saccharides and polyols (FODMAPs), particularly fructans.[2] Both of these non-digestible carbohydrates are well documented to change microbial structure and their metabolic products.[3] Such differences explain not only the differences in the relative abundance of butyrate-producing genera, *Faecalibacterium* and *Blautia*, between the diets but also the differences in faecal concentrations of short-chain fatty acids since non-digestible dietary carbohydrates are the major substrates for these fermentative products.

Furthermore, the authors report differences in protein fermentation between the dietary groups, as shown by differences in faecal amino acid metabolites (indole, indoleacetic acid and p-cresol), despite no difference in protein intake and, therefore, protein substrate availability for the microbes. They conclude that a high-fat diet can reduce colonic protein fermentation independently of fibre or non-digestible carbohydrate intake and imply that this is an effect of the dietary fat. However, they fail to point out that such differences are likely partly or completely secondary to differences in carbohydrate substrate availability due to differences in the intake of resistant starch and fructans.[4 5] Most gut bacteria prefer carbohydrates over protein for their energy supply via fermentation. Furthermore, the ample energy released from increased carbohydrate fermentation promotes bacterial proliferation and growth. This increases requirements for peptides and amino acids for biosynthetic purposes, indirectly reducing protein fermentation, a phenomenon known as the 'nitrogen sink'.[5] In animal and human interventional studies, both resistant starch and fructo-oligosaccharides reduce biomarkers of colonic protein fermentation, including faecal ammonia, phenols and branched-chain fatty acids,[5] and reducing FODMAP intake may increase colonic protein degradation.[6] The addition of a fructan to faecal slurries ex vivo promotes carbohydrate fermentation (increase in both CO_2 and H_2 production) and markedly suppresses the production of hydrogen sulfide (H_2S) from fermentation of a sulfur-containing amino acid, cysteine.[7]

The study from Wan *et al* highlights the care that needs to be taken in interpreting effects of dietary manipulations due to collinearity[5] ; specific alteration of dietary fat cannot be achieved without altering other macronutrients (in this case, carbohydrates) if energy intake is not compromised. What this study has shown so nicely is that a high-fat diet alters the colonic luminal microenvironment, but it has not shown that fat itself is the culprit.

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