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Supplementary information

Macronutrient mixtures and interactions in health and disease

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Macronutrient mixtures and interactions in health and disease

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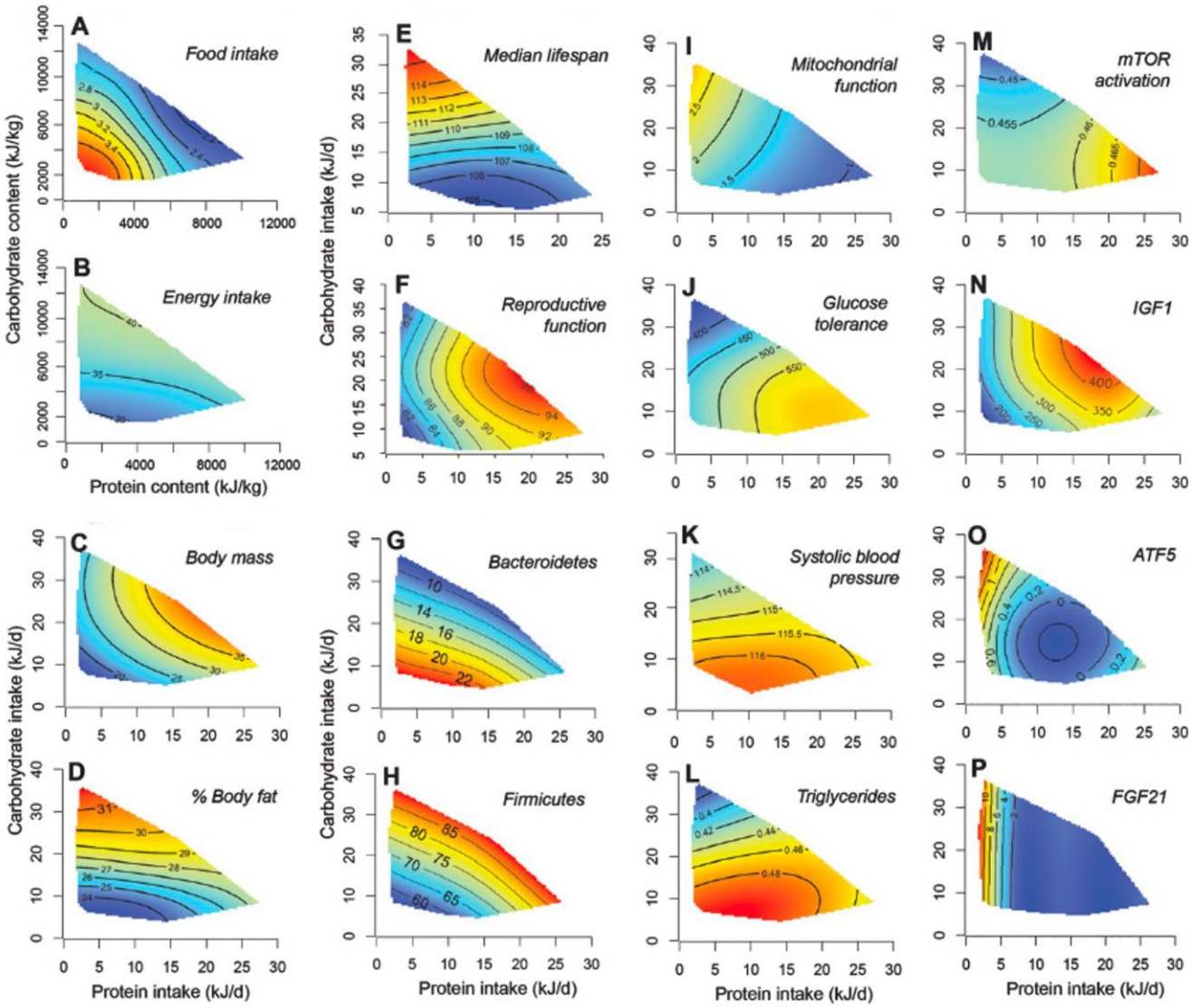
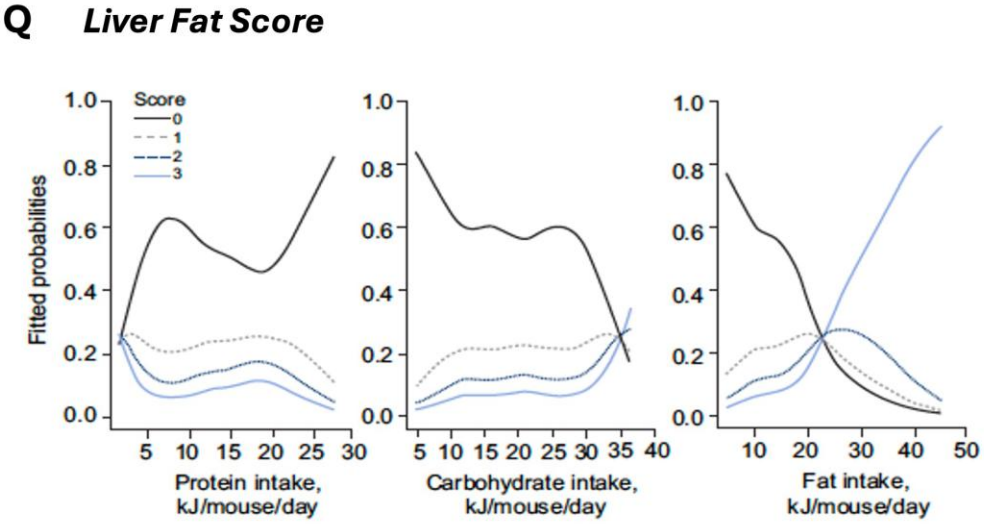
Supplementary information





Supplementary Fig. 1 | Influence of dietary macronutrient composition on intake, physiological, metagenomic and molecular outcomes from a 25-diet study in mice. Data for this figure come from an experiment where male and female mice were placed on one of 25 diets, varying in protein, carbohydrate and fat content, starting from weaning. For illustrative purposes, the figure panels shown here focus on the interaction between protein and carbohydrate. The mice were either culled at 15 months of age for cardiometabolic phenotyping, or allowed to live until natural death to assess lifespan[94]. Each coloured response surface depicts the response to protein and carbohydrate, cut at the median for fat (the full model being fitted to all three macronutrients). Highest levels of a given response variable are indicated in the dark red areas, with the lowest levels represented by the dark blue regions. Panels A and B map food (A) and energy (B) intakes as a function of the concentration (kJ/kg) of protein (x axis) and carbohydrate (y axis) in the diet. As either protein or carbohydrate concentration fell in the diet, food intake increased, indicative of compensatory feeding for both nutrients and shown by the reddening of the coloured response surface. There was limited compensatory feeding for fat (not shown). Compensation for protein was more pronounced than for carbohydrate, consequently, energy intake was greatest on low-protein, high-carbohydrate diets (red area in the top left of panel B). Panels C to P map outcomes as a function of amounts (kJ/day) of protein (x axis) and carbohydrate (y axis) eaten. Panels C and D depict body composition outcomes, showing that lean mass was highest on high-protein, low-carbohydrate diets, whereas percent fat mass was greatest on low-protein, high-carbohydrate diets. Panels E and F highlight the contrasting effects of dietary protein to carbohydrate ratios (P:C) on two key life-history traits: lifespan and reproduction. Mice lived longest on low P:C diets and the shortest on high P:C diets, but displayed the highest reproductive function indicators (male testes mass in this example) on higher P:C diets. Panels G and H depict the response of two major gut microbial taxa to dietary macronutrient content. Panels I to L depict a selection of cardiometabolic measures: (I) liver mitochondrial function, (J) glucose tolerance, (K) systolic blood pressure and (L) plasma triglyceride levels, which show similar (or inverse) surfaces to longevity (E). Panels M to P display components of ageing-associated signalling pathways, in this case in liver. Finally, panel Q depicts the probability of developing different severities of metabolic dysfunction-associated steatotic liver disease

(histological liver lipid score) in older age (y axis) based on protein, carbohydrate, and fat intake (x axis for each respective panel). The highest liver lipid scores were associated with low-protein, high-fat diets. This figure is a composite of panels from figures in two publications[1,2]. ATF5, cyclic AMP-dependent transcription factor ATF-5; FGF21, fibroblast growth factor 21; IGF1, insulin-like growth factor 1; mTOR, serine/threonine-protein kinase mTOR.

References

1. Simpson, S. J. et al. The nutritional geometry of liver disease including non-alcoholic fatty liver disease. *J. Hepatol.* **68**, 316–325 (2018).

2. Simpson, S. J. et al. The Geometric Framework for Nutrition as a tool in precision medicine. *Nutr. Healthy Aging* **4**, 217–226 (2017).