The long-term intake of milk fat does not significantly increase the blood lipid burden in normal and high-fat diet-fed mice

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Background

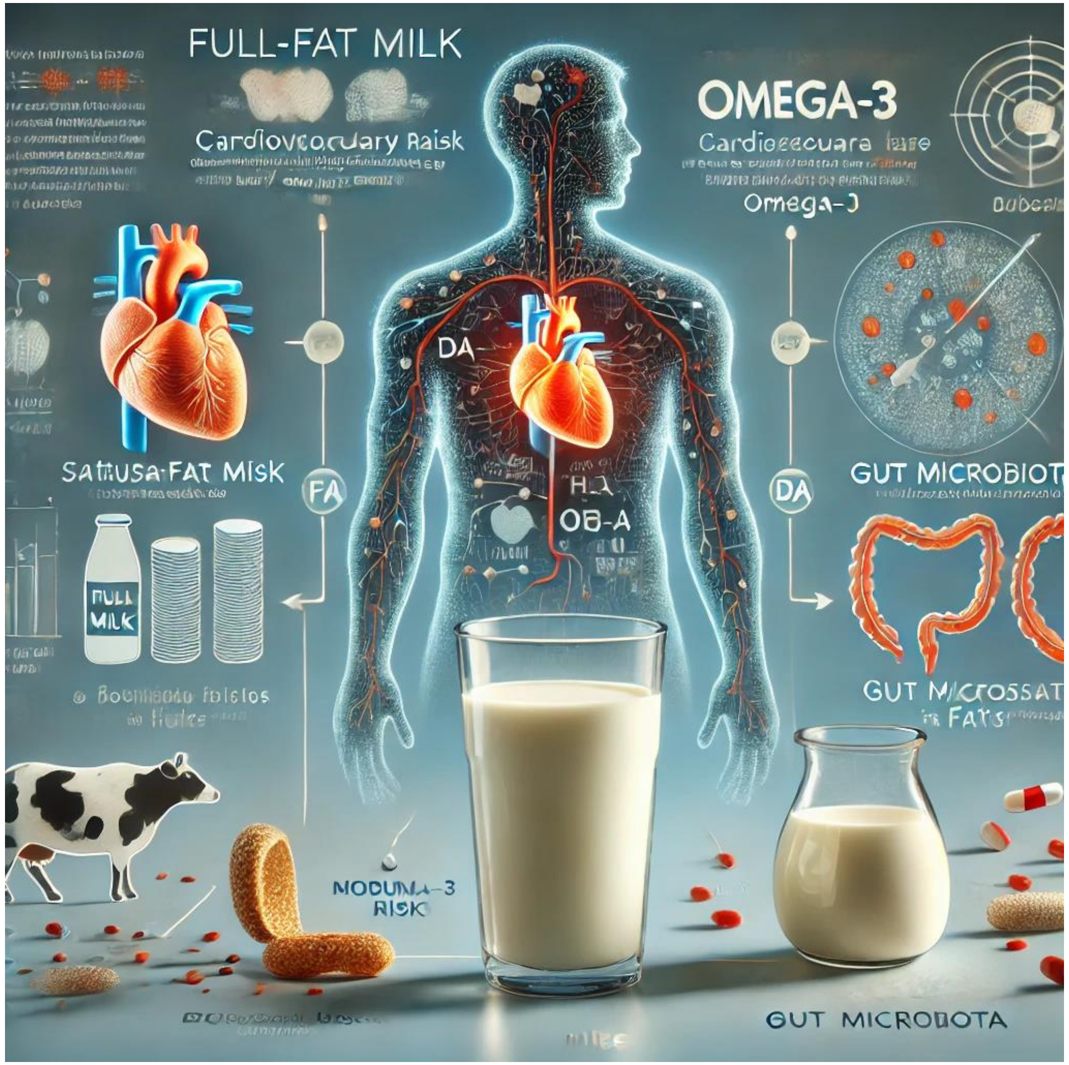
- Milk is one of the most important food sources globally, with a history of consumption spanning thousands of years.

- An increasing body of research suggests that milk fat contains many components beneficial to human health. However, it remains unclear how the synergistic effects of these various beneficial components in milk fat influence host lipid health.

- a large multinational cohort study of individuals enrolled from 21 countries on five continents reported that dairy consumption was associated with a lower risk of mortality and major cardiovascular disease events. Increasing the intake of dairy fat does not increase the risk of CVD and may even reduce the risk of central obesity.

- The gut microbiota (GM) has been implicated in obesity and metabolism. Components of milk can reshape the host's intestinal microenvironment, thereby exerting a certain impact on the secretion network of metabolites throughout the entire gut.

- The relationship between milk fat intake and host lipid metabolism remains controversial. Whether long-term consumption of milk fat increases the lipid burden in both normal and high-fat diets, and whether the gut microenvironment plays a role in this process, are key issues that require further investigation and resolution.



Methods

- **Experimental Design:** 8-week-old SPF male C57BL/6J mice were used in the experiment. Mice were randomly assigned to two groups, the normal diet group (ND) and the high-fat diet group (HFD), and were continuously fed for 10 weeks while monitoring blood lipid indicators. Starting from week 11, the mice were subsequently divided into six subgroups(n=10) for a 7-week intervention: ND control (N-Ctl), ND whole milk (N-Mlk), ND milk fat (N-Fat), HFD control (H-Ctl), HFD whole milk (H-Mlk) and HFD milk fat (H-Fat).
- **Normal diet, high-fat diet and milk-related components:** whole milk subgroup mice were given 15 mL/day of pasteurized milk. The milk fat subgroup received 0.5 ml/day of fat via intragastric gavage. Whey protein, lactoferrin, and casein were administered via gavage to the respective subgroups at concentrations of 54 mg/mL, 33 mg/mL, and 48 mg/mL.
- **Data analysis:** Mouse body weight, blood lipid levels, adipose tissue, gut microbiota, and fecal metabolites were collected at designated time points. The data were split into training and test sets at a 9:1 ratio and used for model development through 20 iterations to train and validate machine learning algorithms, aiming to explore the long-term effects of milk fat on host lipid metabolism.

(A)

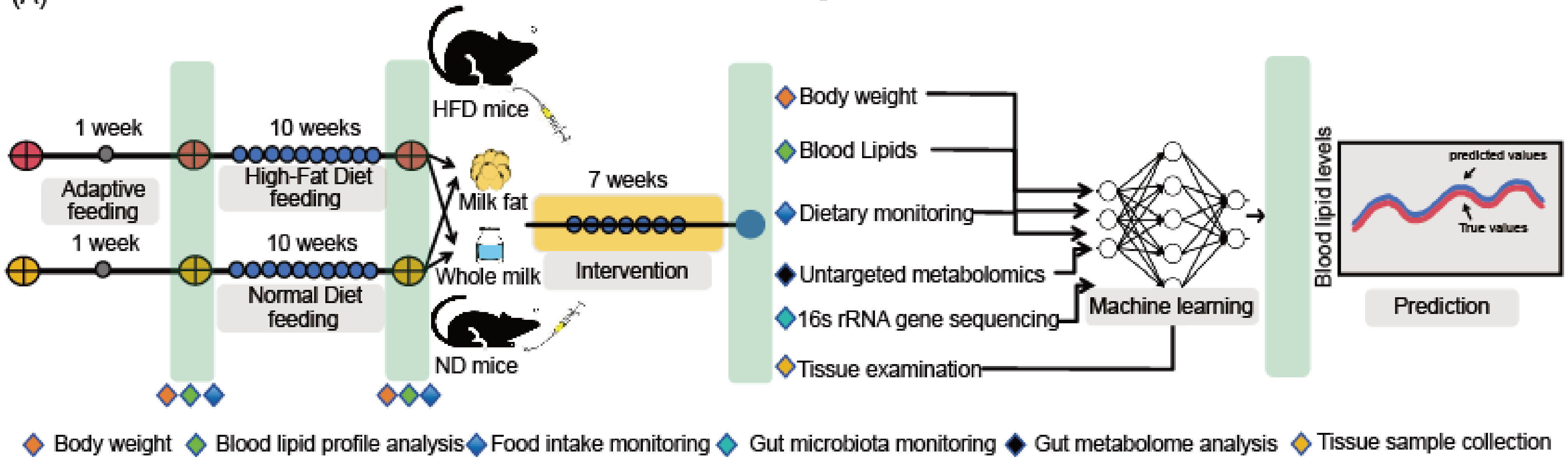
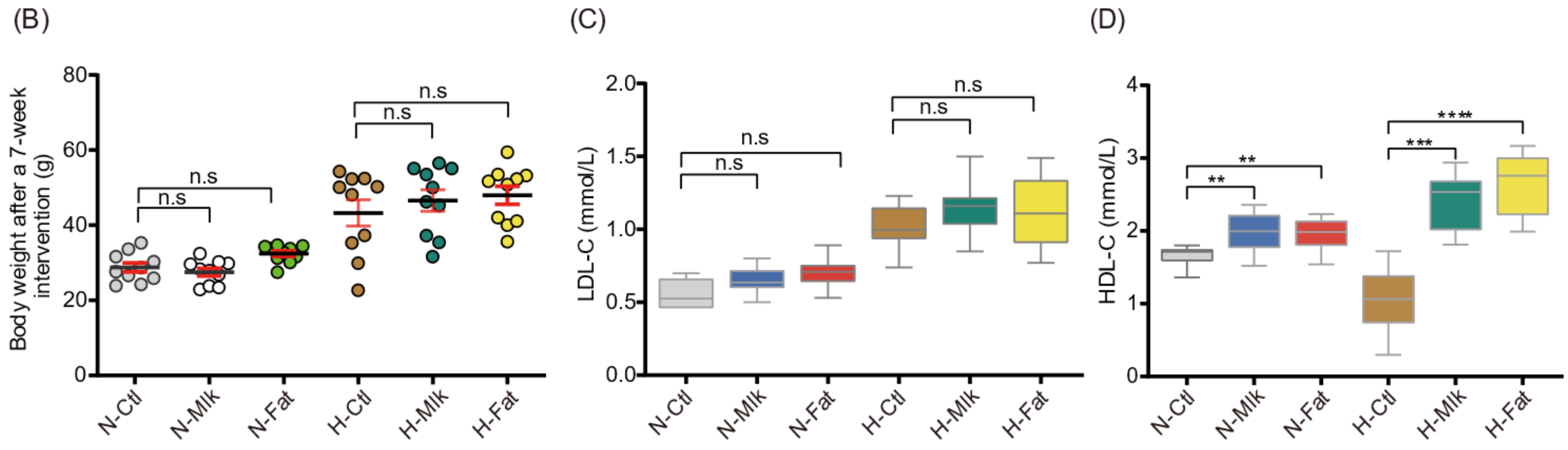


Figure 1(A)： Effects of long-term intake of milk fat and whole milk on blood lipid levels and gut microbiota in mice fed a normal diet or a high-fat diet.

Results

Effects of long-term milk fat intake on lipid profiles in mice fed normal and high-fat diets



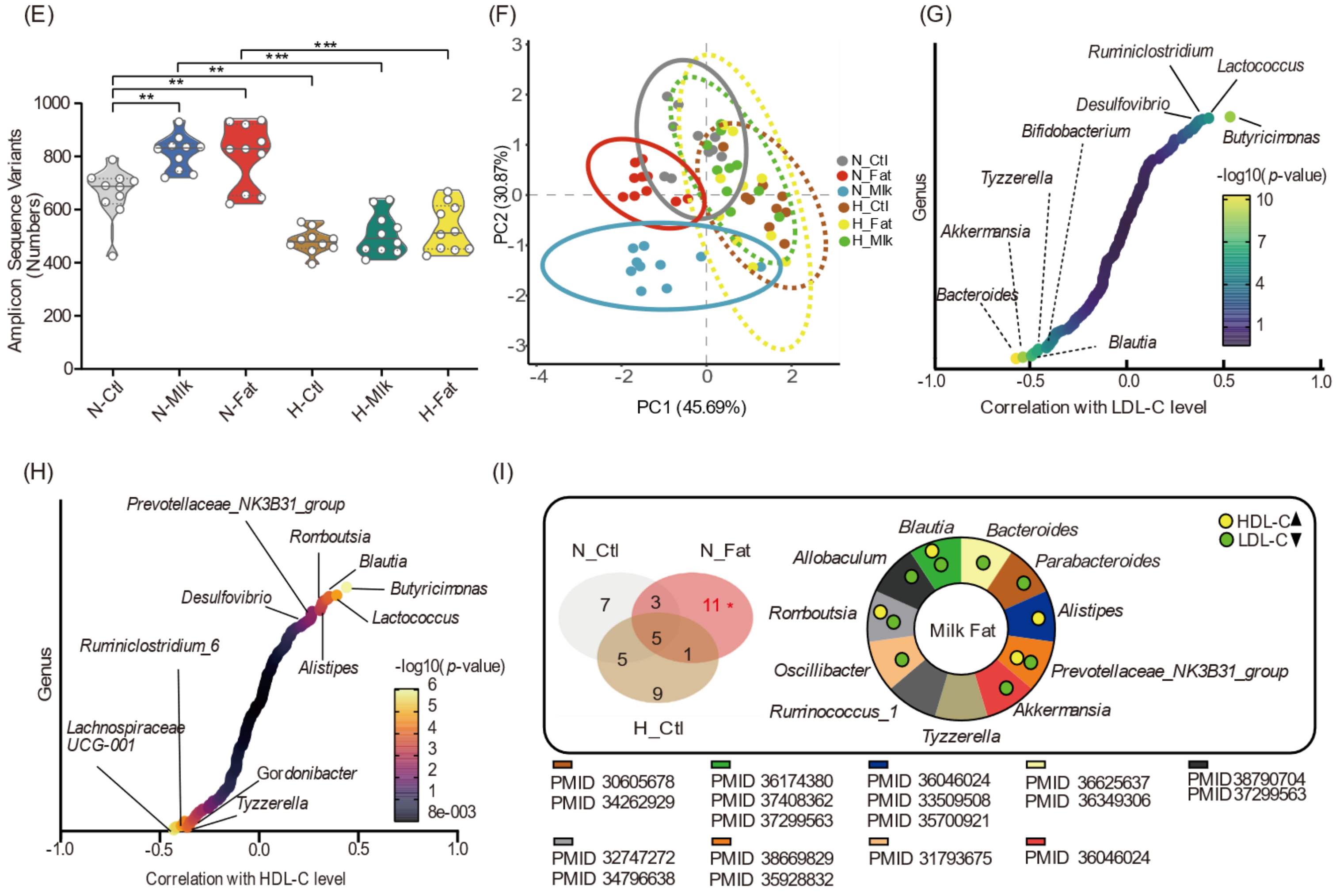
After 7 weeks of milk fat and whole milk intervention in normal diet (ND) and high-fat diet (HFD) mice:

- The weight changes of mice in the six subgroups showed that long-term intake of milk fat and whole milk did not cause significant differences in body weight.
- Long-term intake of milk fat and whole milk did not result in significant changes in peripheral blood LDL-C levels.
- Long-term intake of milk fat and whole milk significantly increased the levels of peripheral blood HDL-C.

Figure 1(B-D)： Effects of long-term intake of milk fat and whole milk on blood lipid levels and gut microbiota in mice fed a normal diet or a high-fat diet.

Results

Milk fat can bidirectionally regulate peripheral LDL-C and HDL-C levels by targeting key gut bacteria

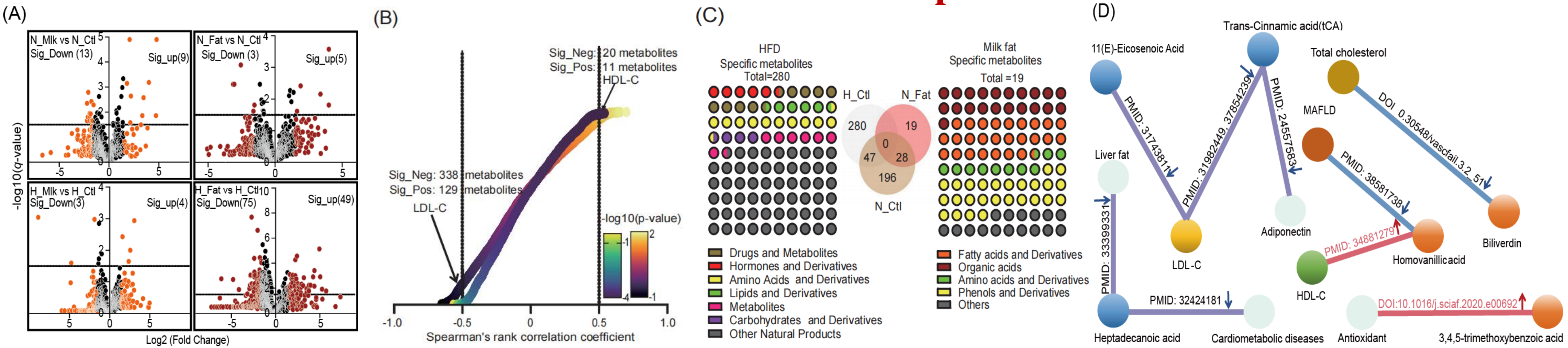


- Long-term intake of milk fat and whole milk significantly increased the number of intestinal microbiome amplicon sequence variants (ASVs) in both ND and HFD mice.
- HFD significantly altered the host gut microbiota structure.
- Long-term intake of milk fat and whole milk reshaped the gut microbiota structure in ND mice but was insufficient to improve the gut microbiota structure in HFD mice.
- Several gut bacteria were significantly correlated with host LDL-C and HDL-C levels.
- The 11 unique differential bacteria induced by milk fat could bidirectionally regulate peripheral blood LDL-C and HDL-C levels to varying degrees.

Figure 1(E-I)： Effects of long-term intake of milk fat and whole milk on blood lipid levels and gut microbiota in mice fed a normal diet or a high-fat diet.

Results

Milk fat influences the intestinal metabolite profile and the differential metabolites modulate host blood lipid metabolism

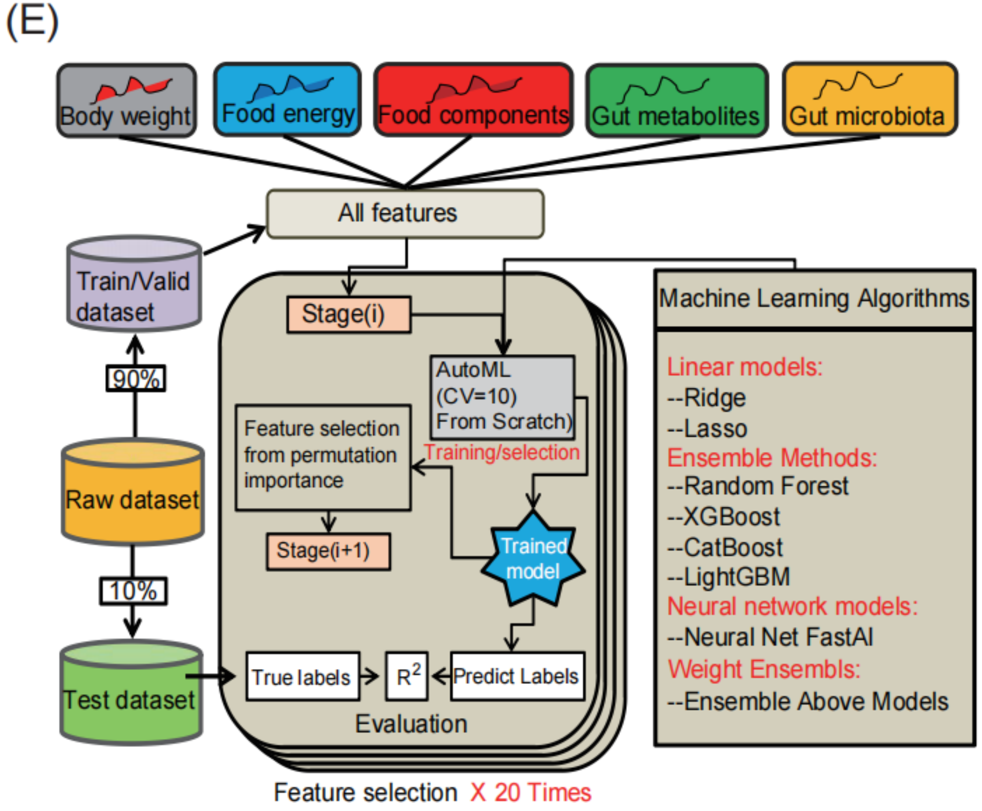


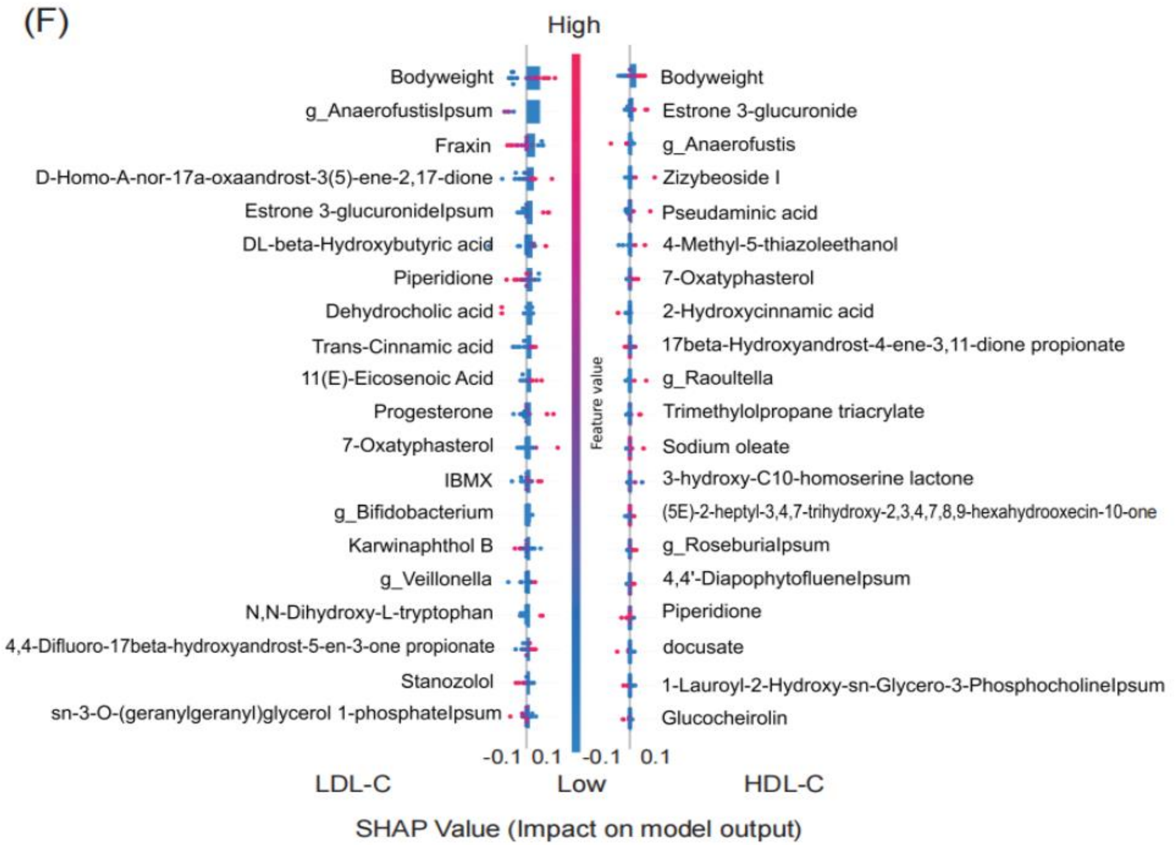
- In ND mice, long-term intake of milk fat significantly downregulated 3 metabolites and significantly upregulated 5 metabolites; long-term intake of whole milk significantly downregulated 13 metabolites and significantly upregulated 9 metabolites.
- In HFD mice, long-term intake of milk fat significantly downregulated 75 metabolites and significantly upregulated 49 metabolites; long-term intake of whole milk significantly downregulated 3 metabolites and significantly upregulated 4 metabolites.
- Twenty metabolites were significantly negatively correlated with host LDL-C, and 11 metabolites were significantly positively correlated with LDL-C; 338 metabolites were significantly negatively correlated with LDL-C, and 129 metabolites were significantly positively correlated with LDL-C.
- Milk fat could induce 19 unique differential metabolites, among which 6 metabolites were involved in the bidirectional regulation of LDL-C and HDL-C.

Figure 2(A-D): Milk fat and whole milk shape the gut metabolome and enable machine learning-based prediction of host lipid levels using gut microbiota and fecal metabolome data.

Results

Predicting lipid changes using an optimized machine learning algorithm with reshaped gut microbiota and metabolites



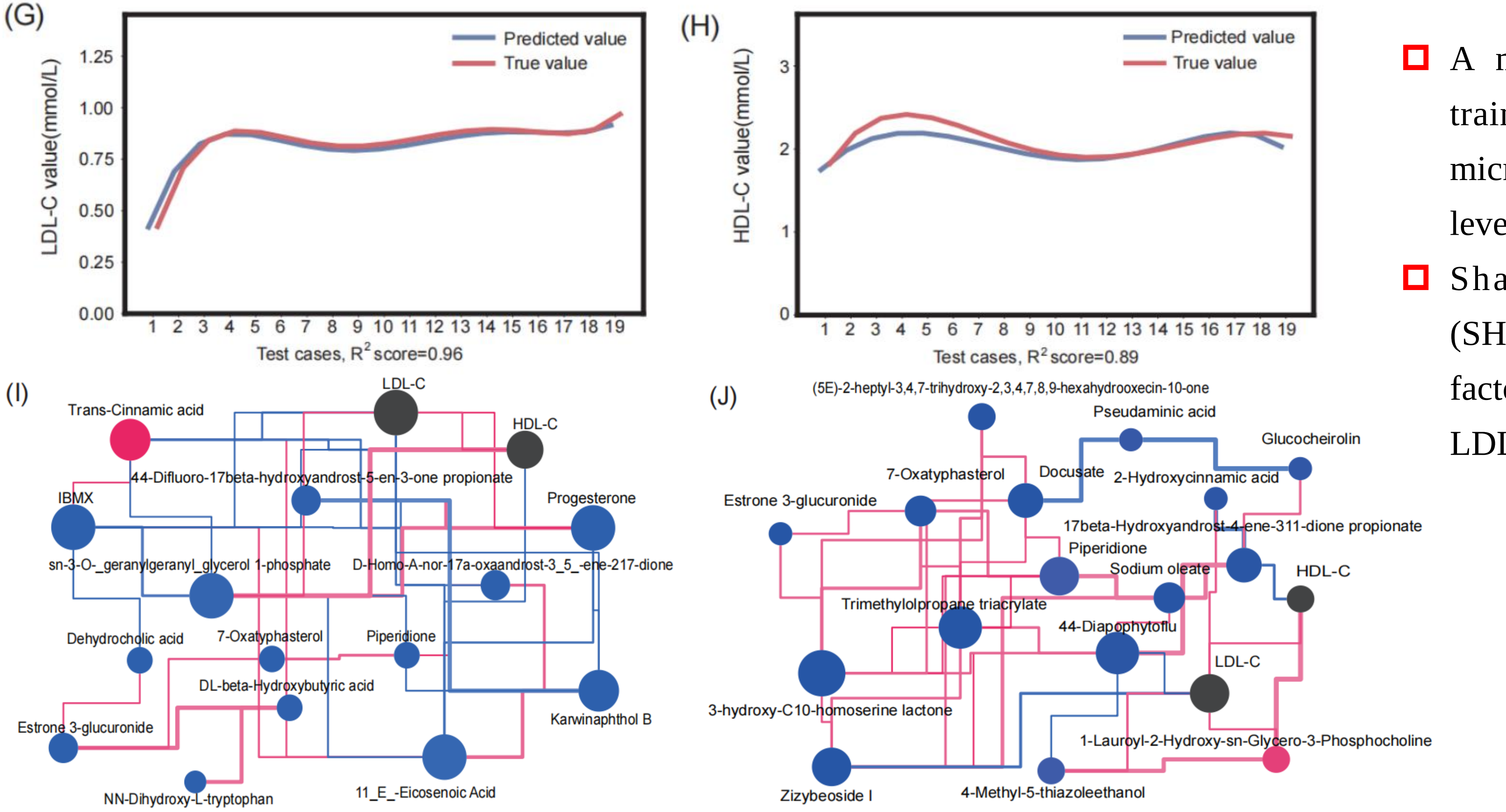


- A machine learning model was trained using gut metabolites and microbiome structure to predict lipid levels.
- Shapley Additive Explanation (SHAP) analysis identified 20 key factors that influence the accuracy of LDL-C and HDL-C predictions.

Figure 2(E-F): Milk fat and whole milk shape the gut metabolome and enable machine learning-based prediction of host lipid levels using gut microbiota and fecal metabolome data.

Results

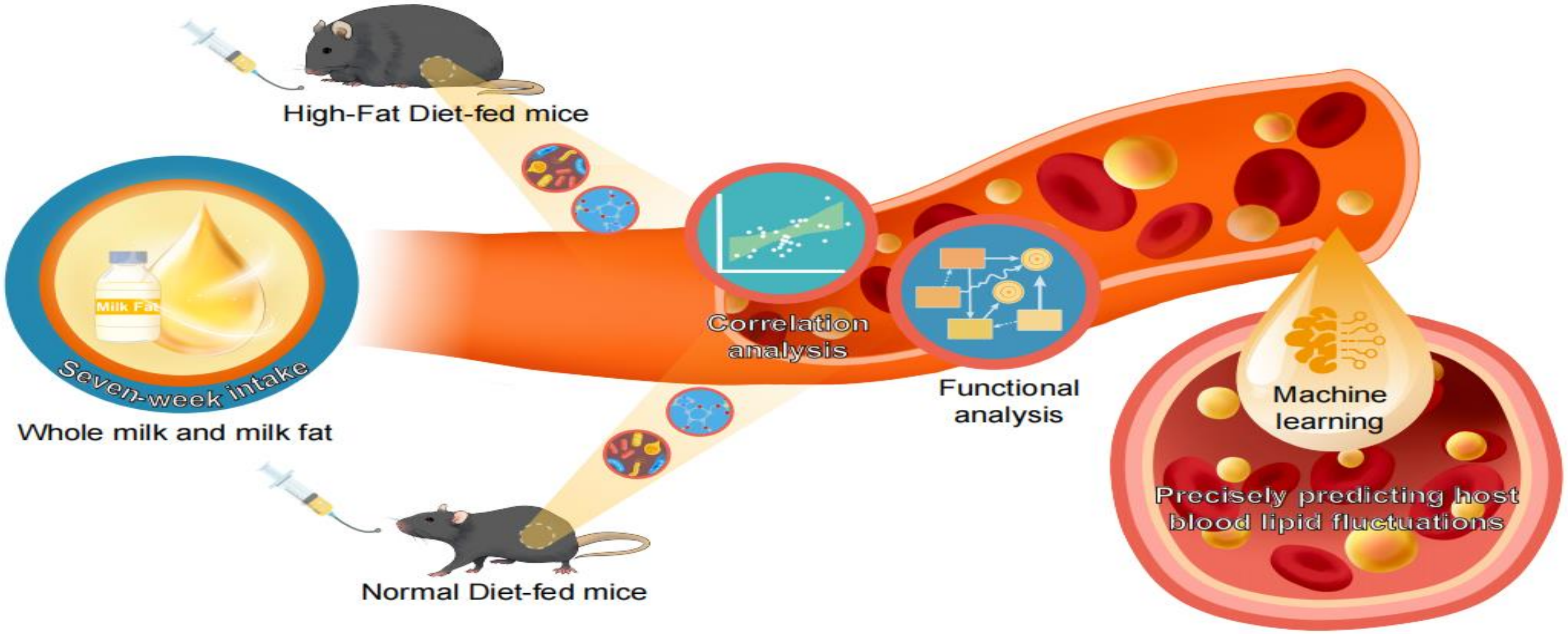
Predicting lipid changes using an optimized machine learning algorithm with reshaped gut microbiota and metabolites



- A machine learning model was trained using gut metabolites and microbiome structure to predict lipid levels.
- Shapley Additive Explanation (SHAP) analysis identified 20 key factors that influence the accuracy of LDL-C and HDL-C predictions.

Figure 2(G-J): Milk fat and whole milk shape the gut metabolome and enable machine learning-based prediction of host lipid levels using gut microbiota and fecal metabolome data.

Conclusion



- Long-term intake of milk fat and whole milk does not significantly increase the lipid burden in normal and high-fat diet mice.
- Gut microbiota and metabolites regulated by milk fat and whole milk can accurately predict lipid levels based on optimized machine learning algorithms.
- These findings provide new insights into understanding the effects of milk fat and whole milk on lipid metabolism, offering new perspectives for the development of global nutrition policies and precision nutrition improvements.

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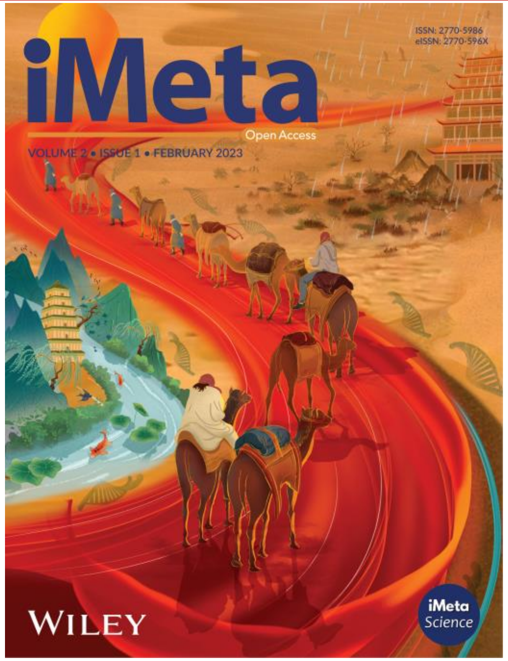

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