A gut microbiome-lipid axis in early pregnancy is associated with metabolic dysregulation and diabetes risk

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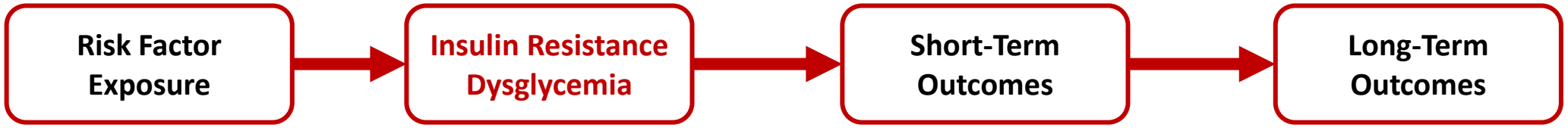
Background

GDM Affects Both Mothers and Offspring



	Pregnancy	Birth	Postpartum	
Mother	Preeclampsia	Difficult Delivery	Diabetes	~10-fold
Child	Fetal Growth Restriction	Adverse Birth Outcomes	Growth Impairment, CVD, T2DM	

Early-pregnancy changes may precede GDM diagnosis

Highlights

- First-trimester microbiome and lipidome profiles revealed early molecular signatures preceding GDM diagnosis.
- Integrated analyses linked *Ruminococcus bicirculans* to GDM-related metabolic dysregulation through glycosphingolipid metabolism.
- Animal and cell experiments showed that *Ruminococcus bicirculans* and LacCer 24:1 improved insulin tolerance and modulated hepatic AKT signaling.
- Combined microbial and lipid risk scores identified women at high GDM risk in early pregnancy.

Study Design

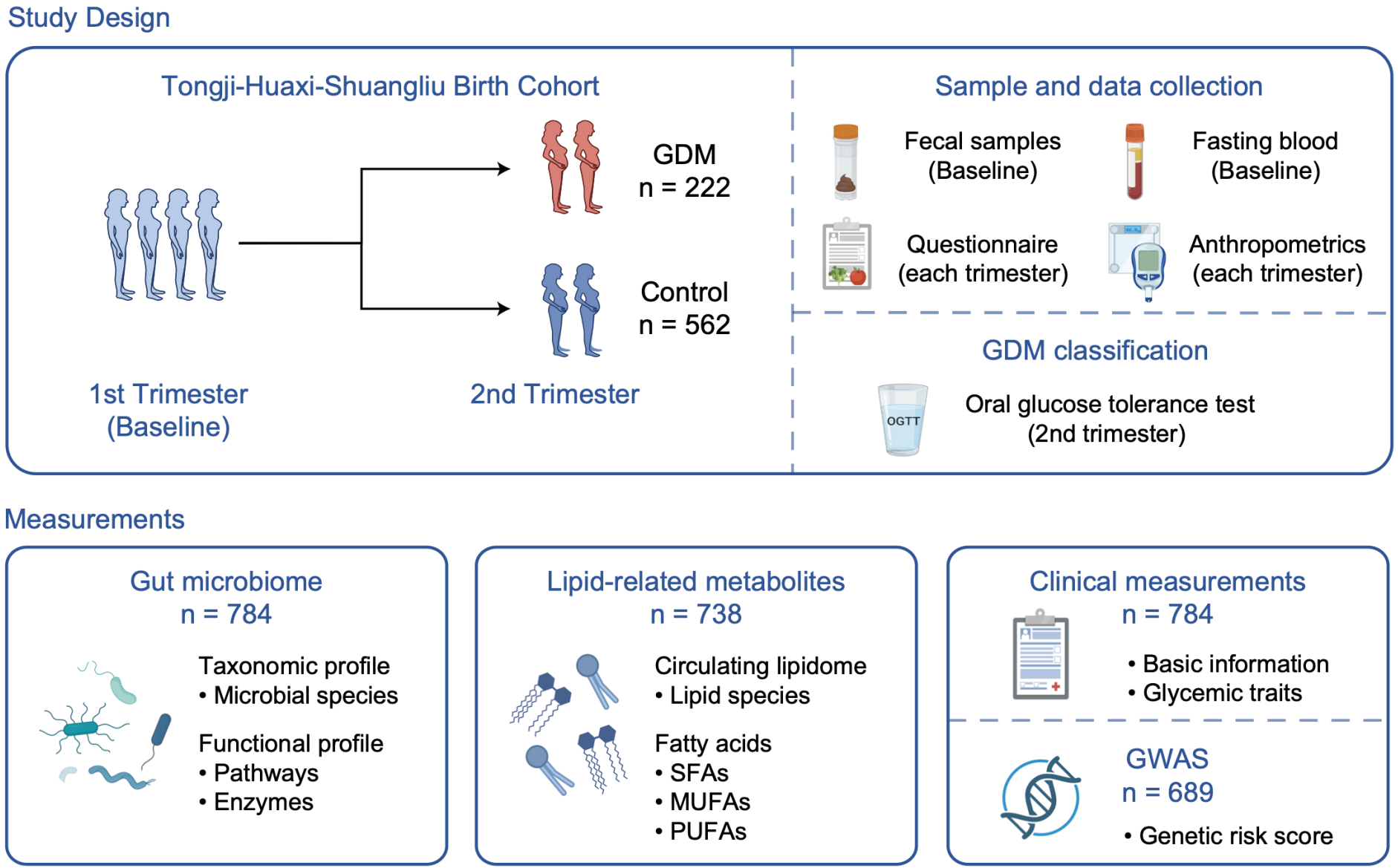
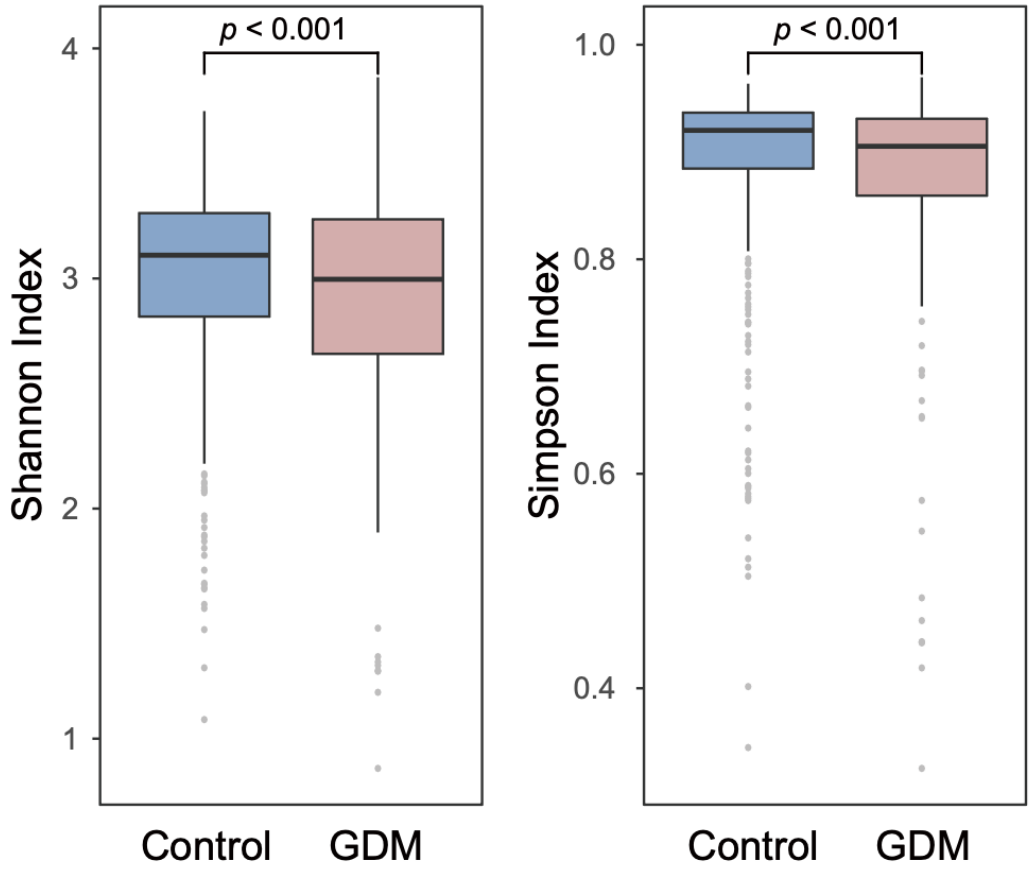


Figure 1. Study design, multi-omics measurements, and analytical framework.

Gut Microbiome Alterations Precede GDM Diagnosis

Gut Microbial Diversity



Gut Microbial Community Structure

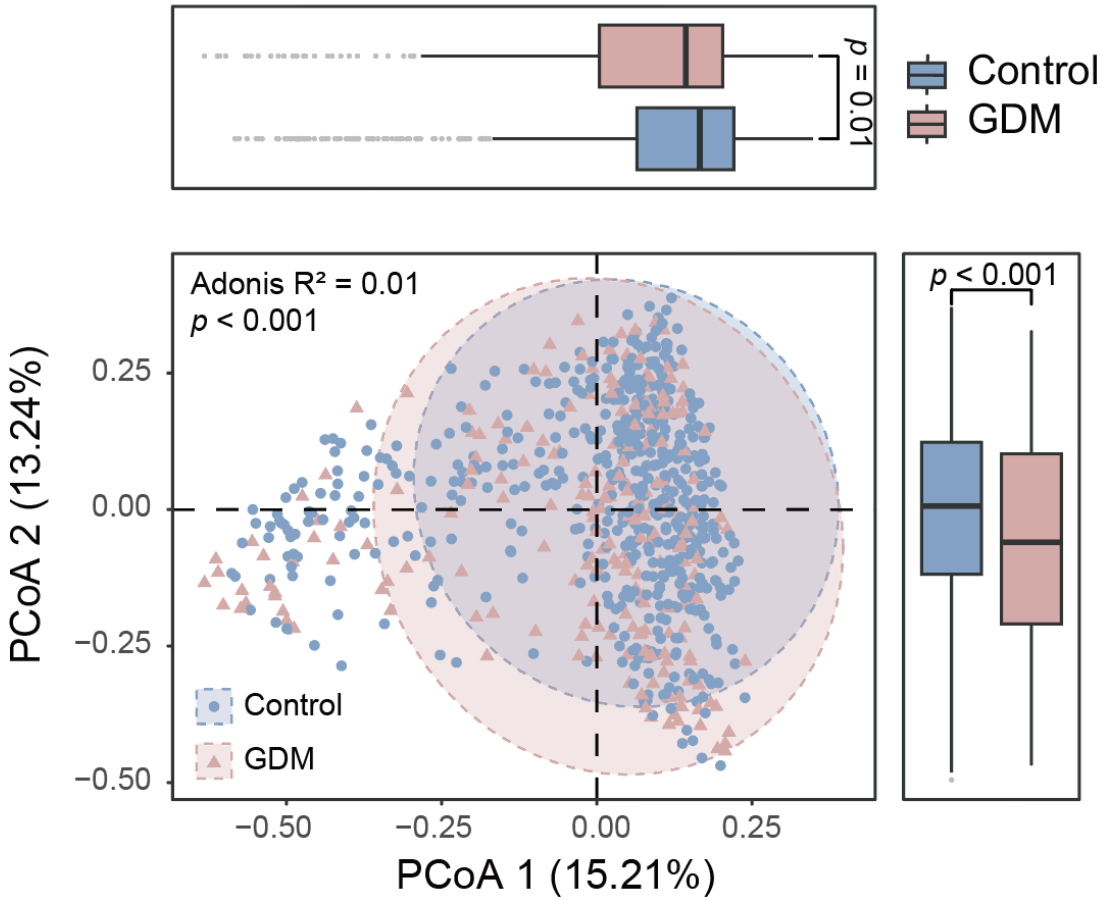
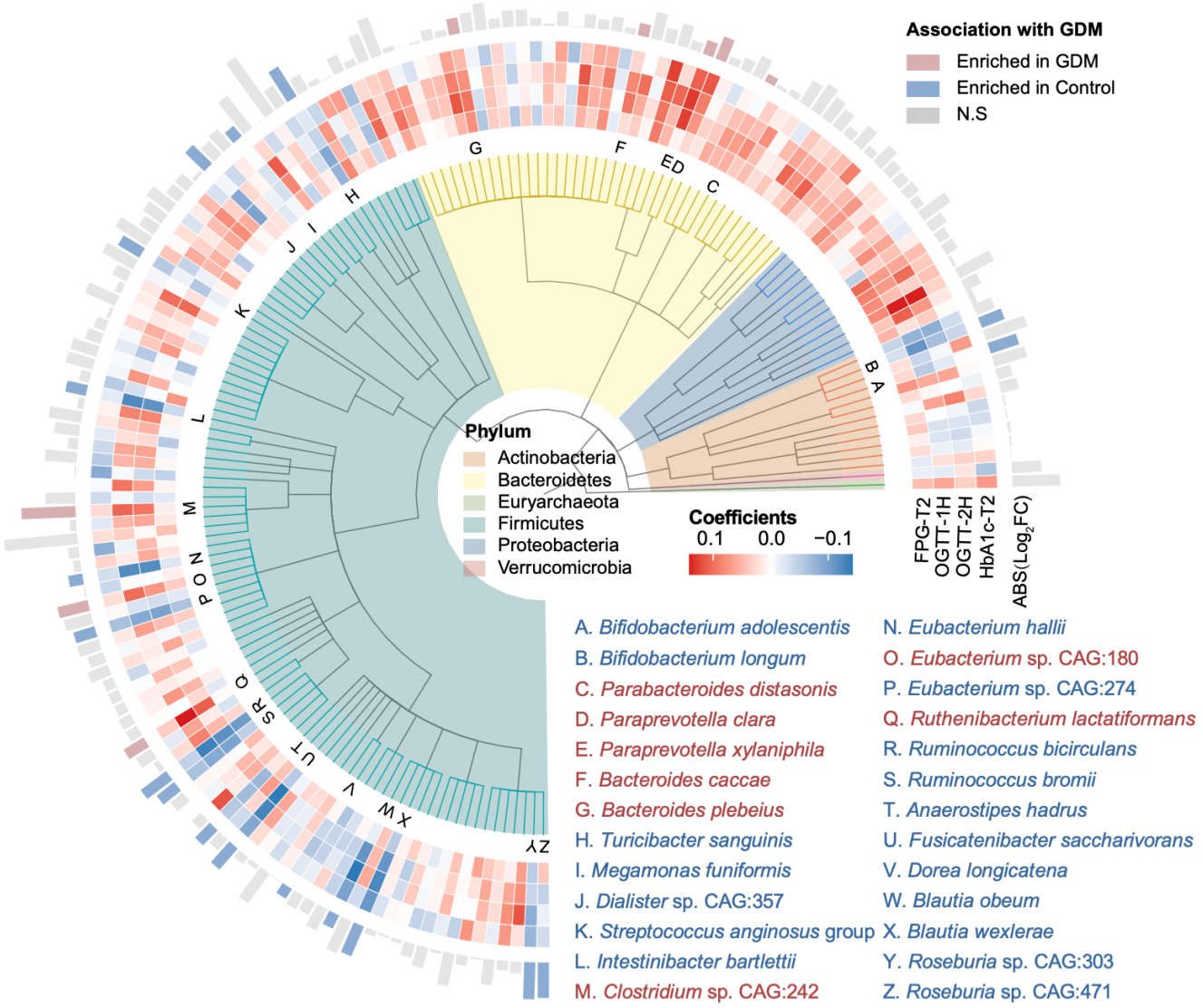


Figure 2A-B. Early-pregnancy gut microbial diversity and composition in relation to later GDM.

Twenty-six Microbial Species Are Associated with GDM Risk

GDM-Associated Microbial Taxa



Concordance across Populations

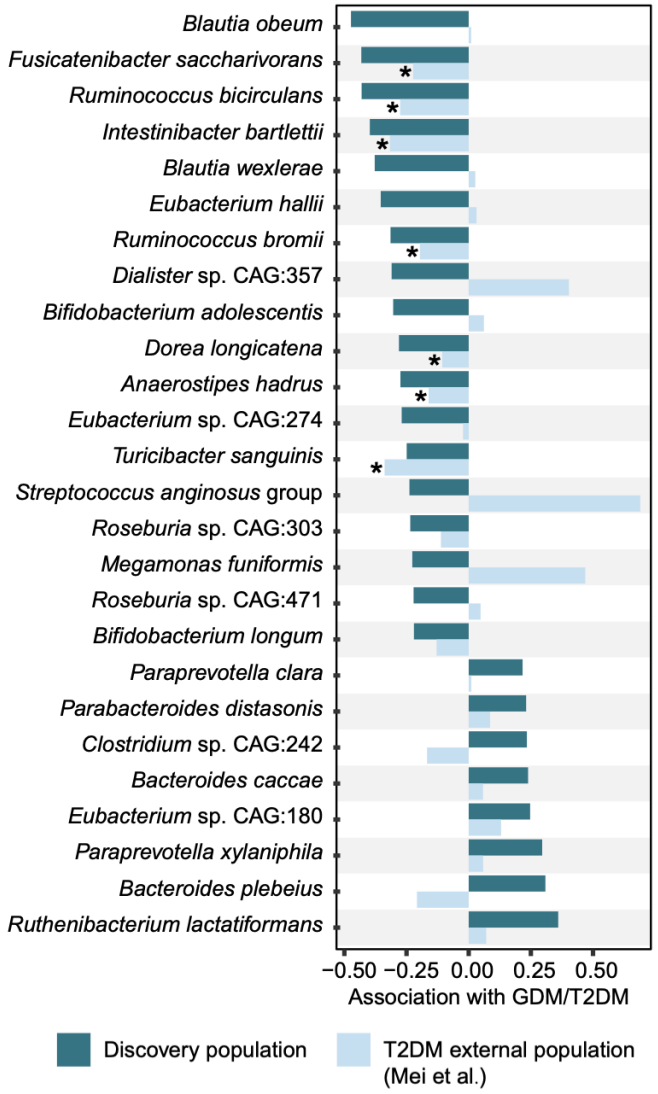
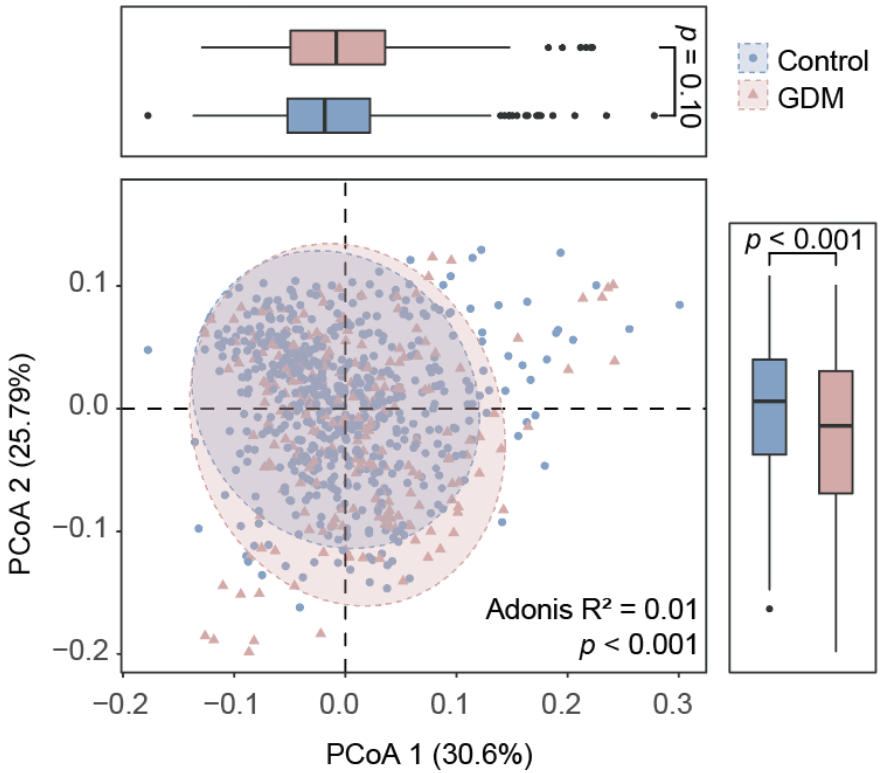


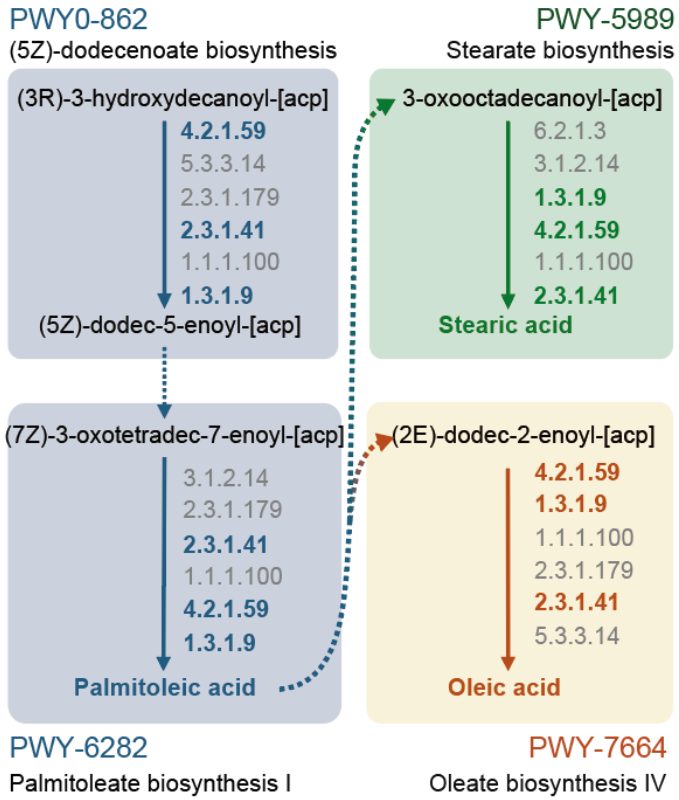
Figure 2D-E. Microbial species associated with later GDM and concordance across populations.

Microbial Functions Shift toward Lipid Biosynthesis

Microbial Functional Profile



Fatty Acid Biosynthesis Pathways



Key Enzymes and Circulating Fatty Acids

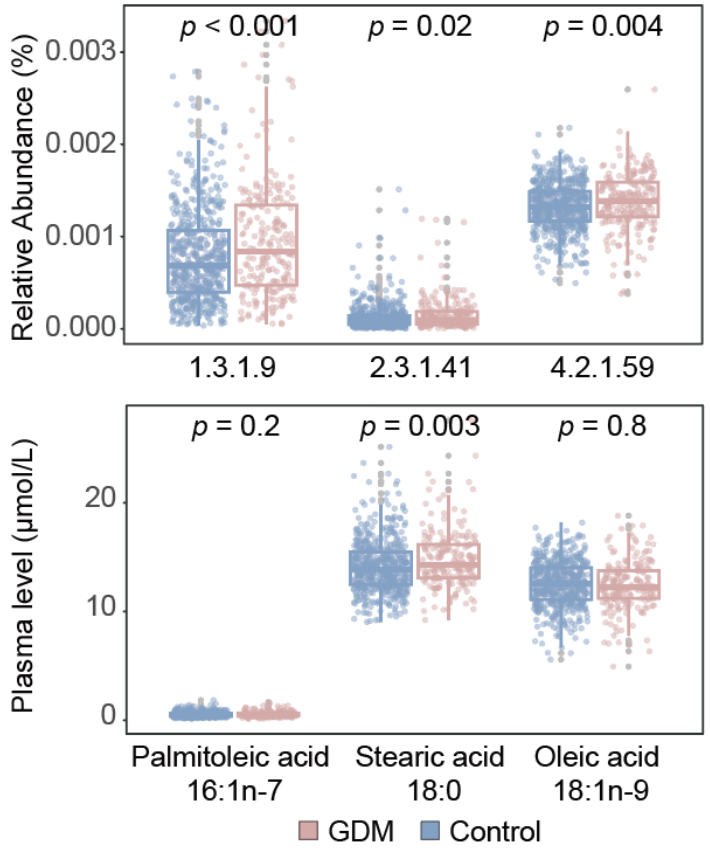
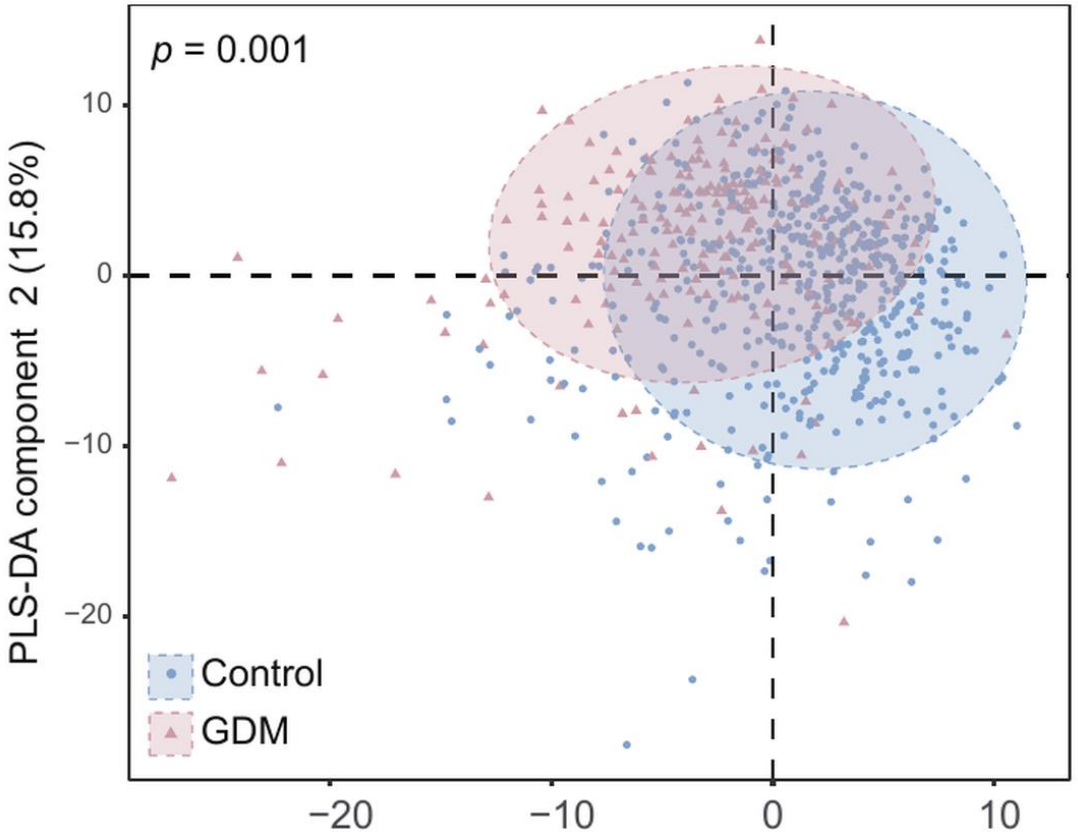


Figure 3A-E. Microbial functional features linked to the risk of later GDM.

Plasma Lipidome Is Remodeled Before GDM Diagnosis

Overall Lipidomic Profile



Lipid Classes and GDM Risk

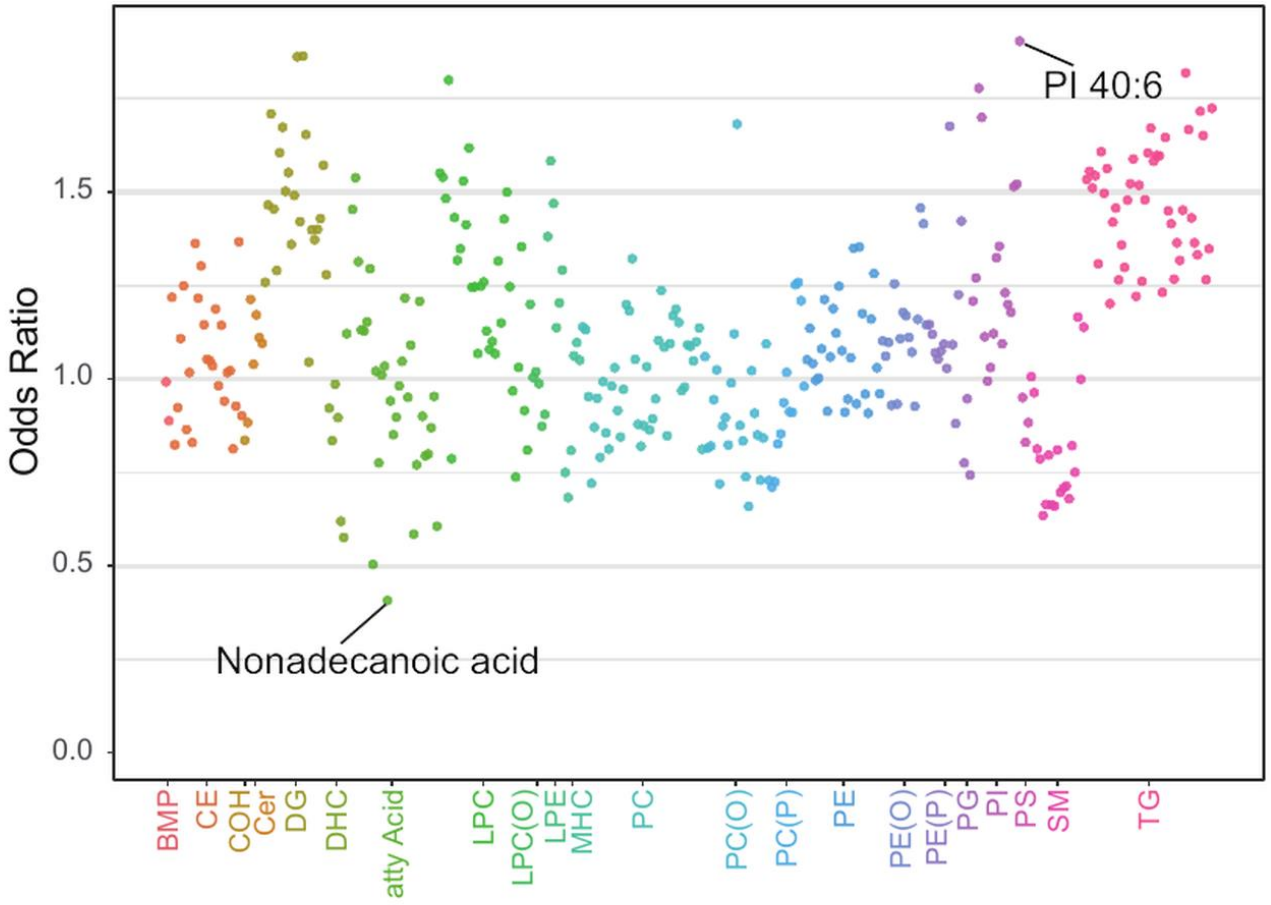
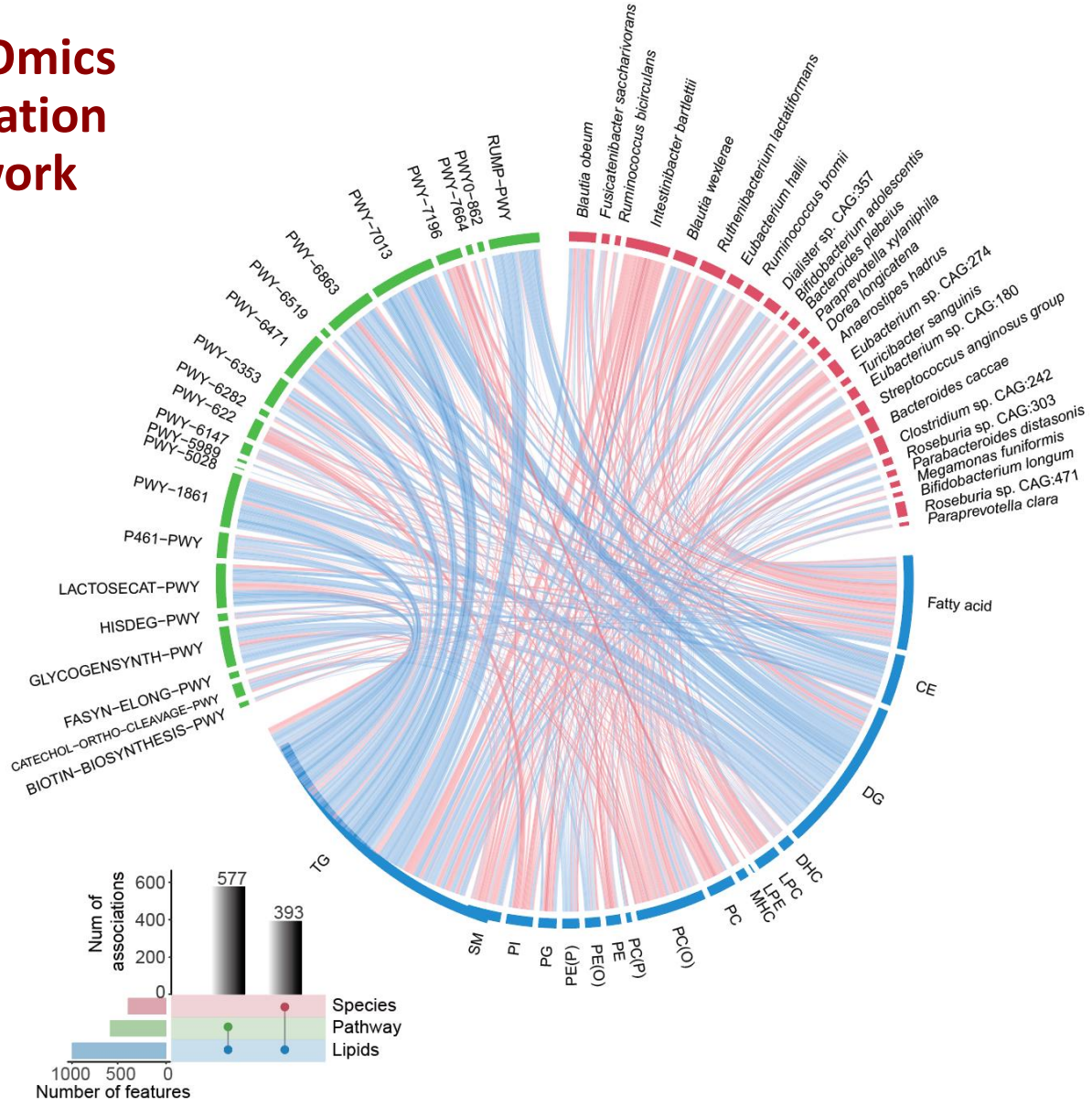


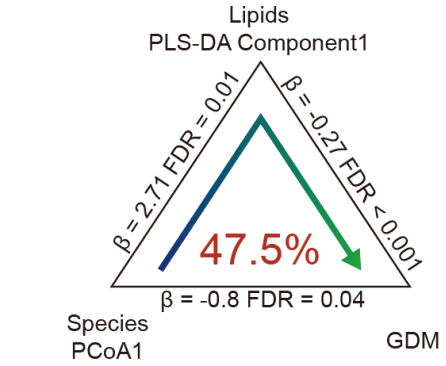
Figure 4A-B. Early-pregnancy plasma lipidomic alterations associated with later GDM.

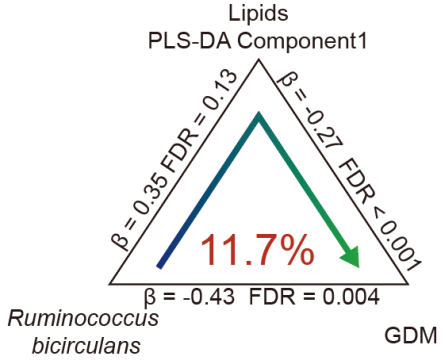
Microbial Changes Are Associated with Host Lipid Alterations

Cross-Omics Association Network



Lipidomic Mediation





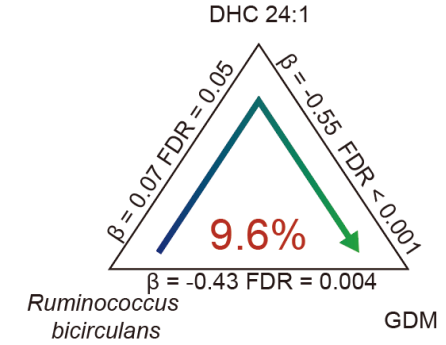


Figure 4C, G-I. Cross-omics microbiome-lipid associations and lipidomic mediation effects.

R. bicirculans Produces LacCer 24:1 Anaerobically

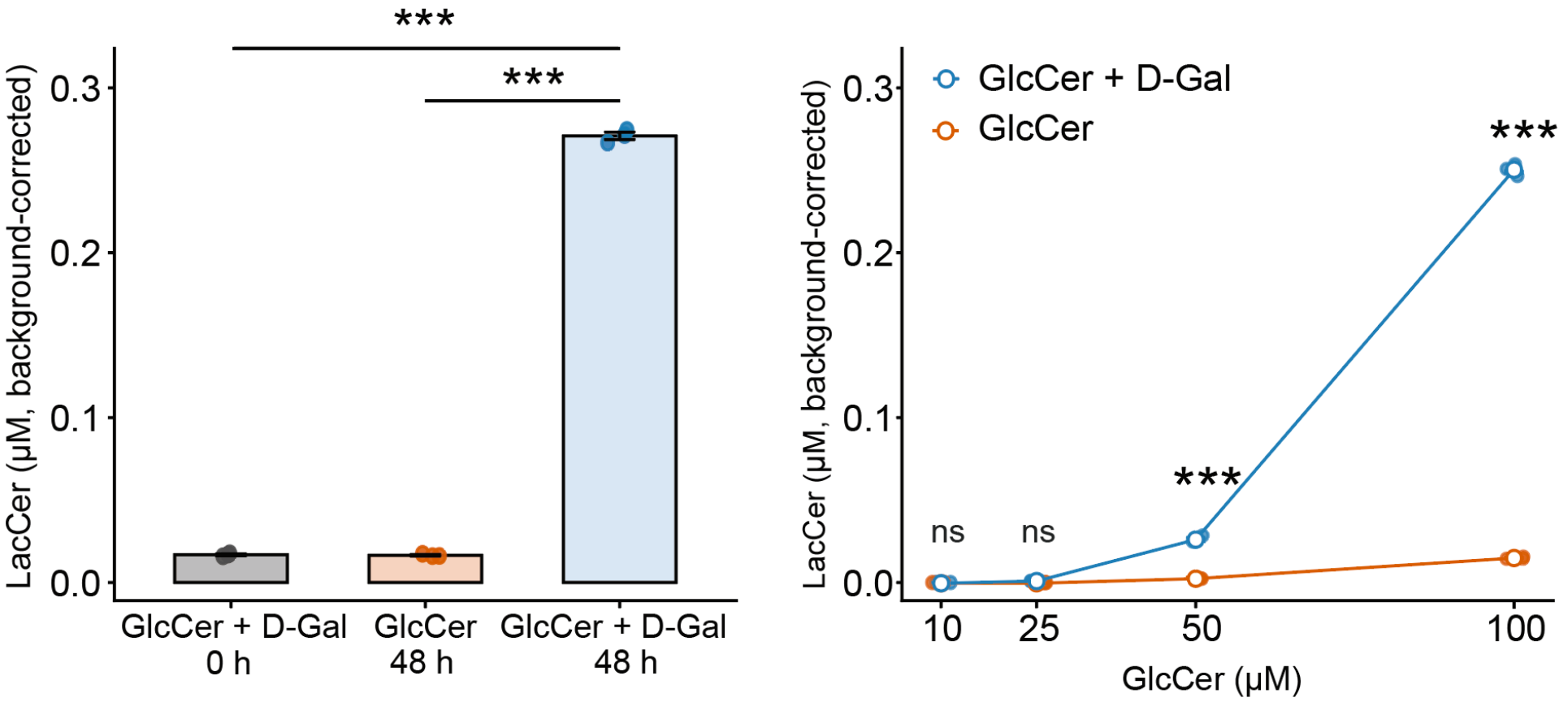
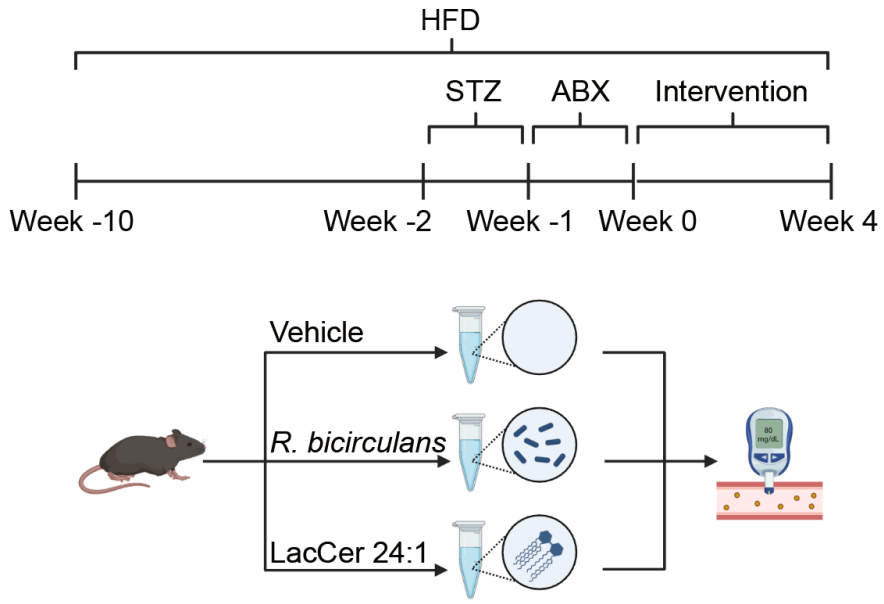
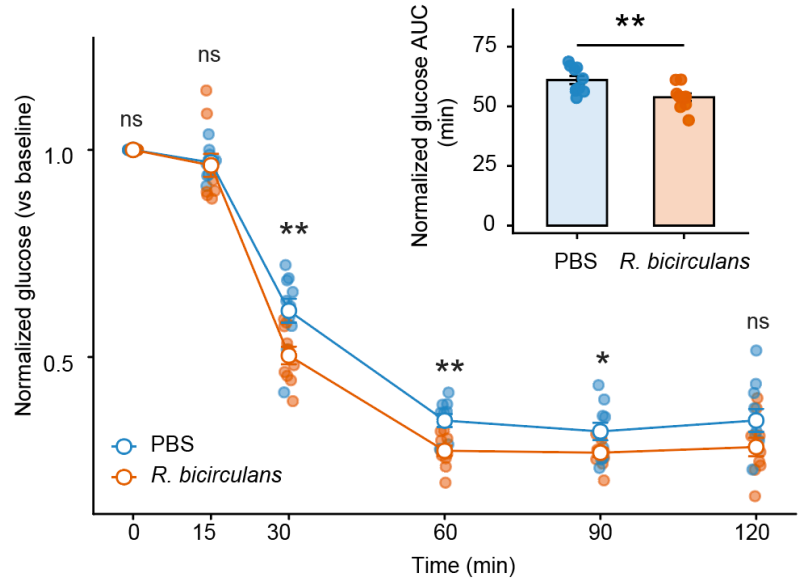


Figure 5A-B. Anaerobic production of LacCer 24:1 by *R. bicirculans*.

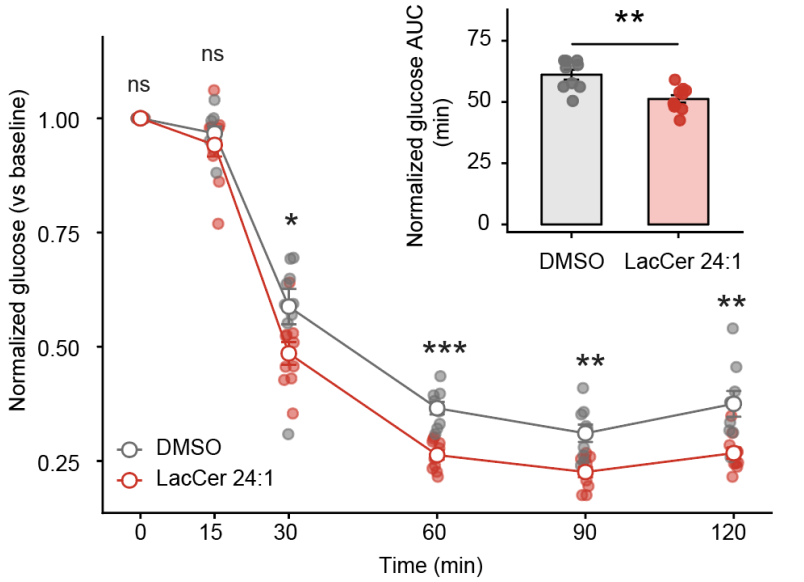
R. bicirculans and LacCer 24:1 Improve Insulin Tolerance

Animal Study Design





Bacterial Colonization

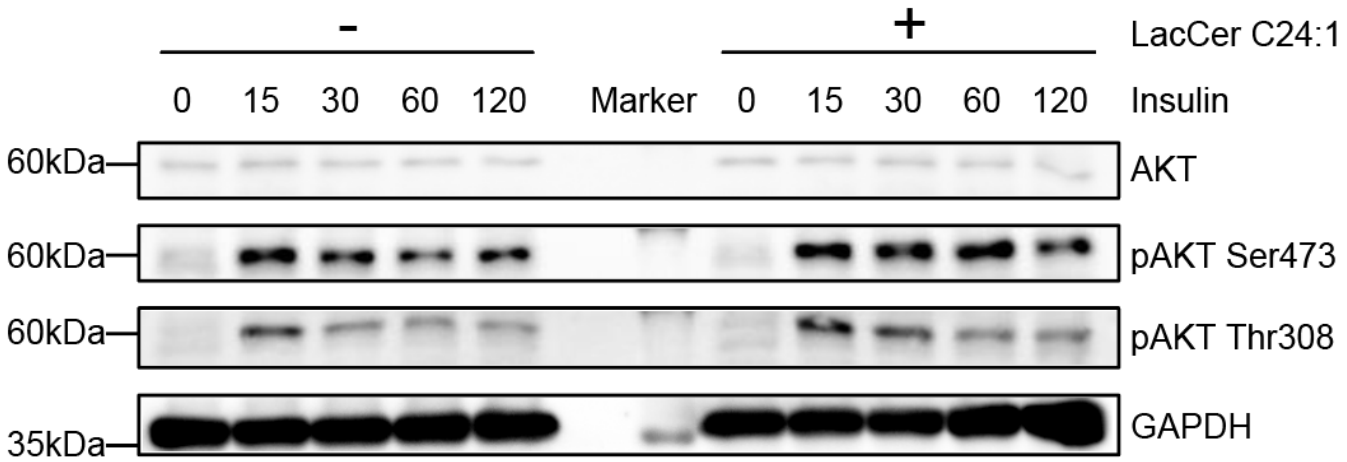


LacCer 24:1 Administration

Figure 5C-E. *R. bicirculans* colonization or LacCer 24:1 administration improves insulin tolerance in mice.

LacCer 24:1 Modulates Hepatic AKT Signaling

AKT Phosphorylation



Microbe–Lipid Link to Insulin Signaling

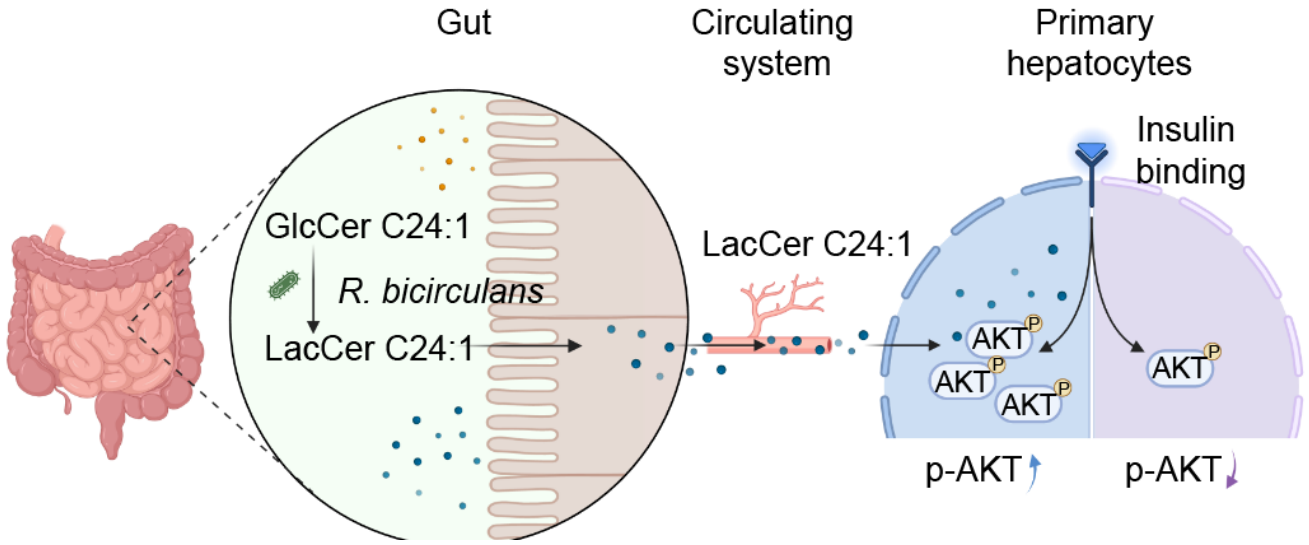


Figure 5F-G. LacCer 24:1 modulates AKT phosphorylation in primary hepatocytes and the proposed model.

Multi-Omics Integration Improves GDM Discrimination

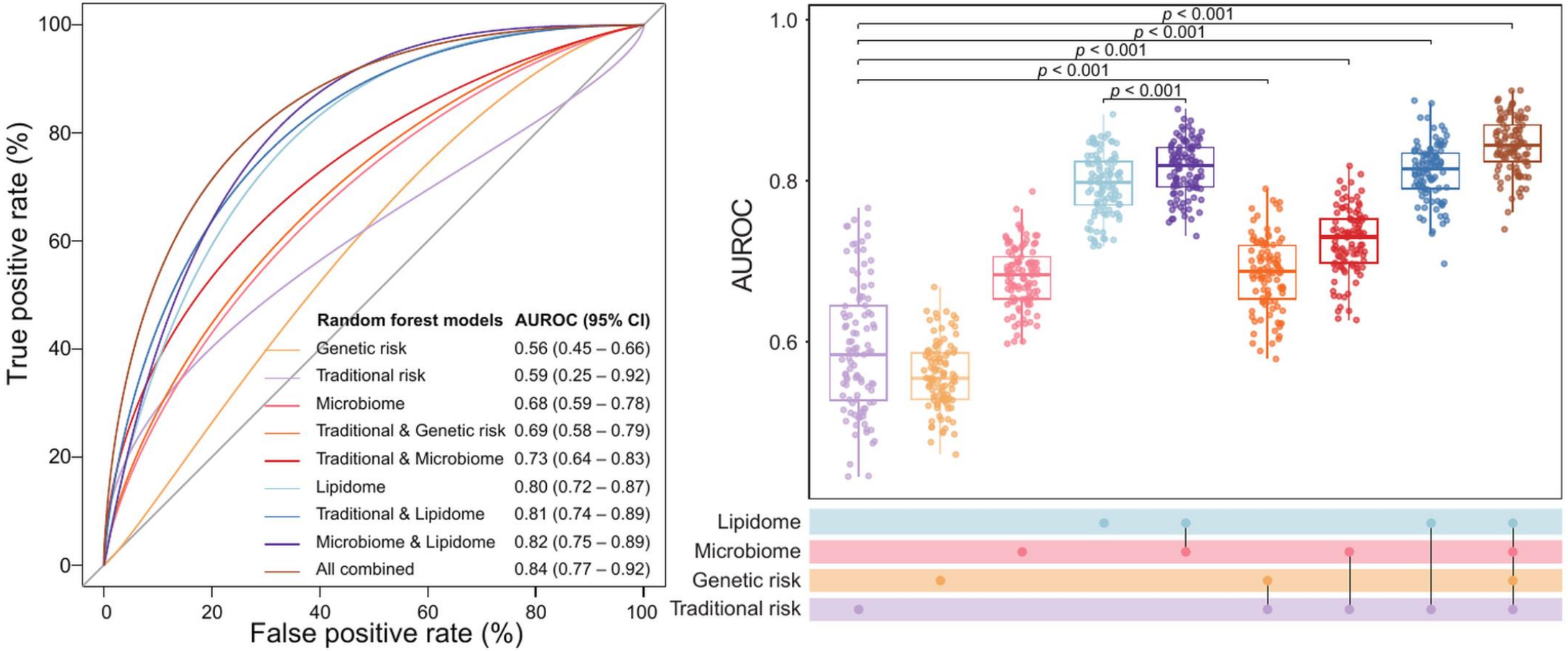
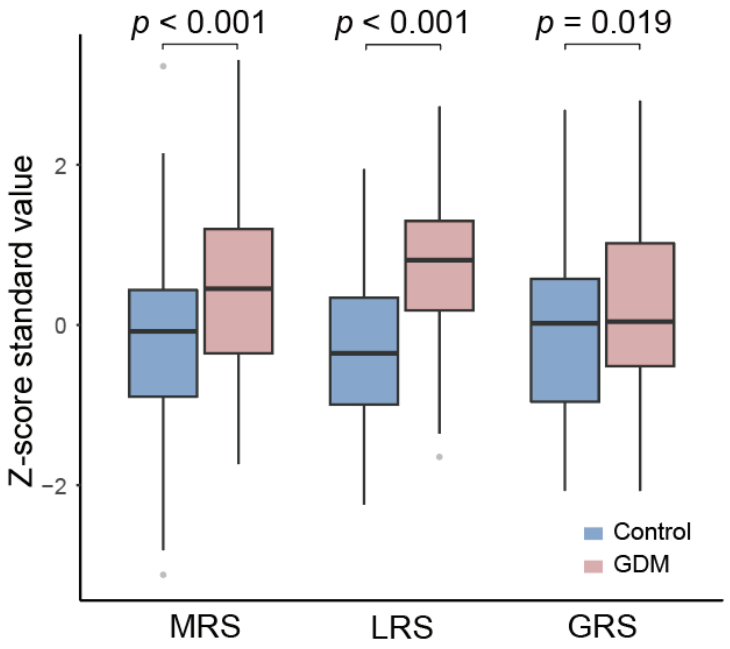


Figure 6A-C. Integrating microbiome and lipidomic features improves early-pregnancy discrimination of later GDM.

Microbial and Lipid Scores Identify High-Risk Women

Microbial, Lipid, and Genetic Scores

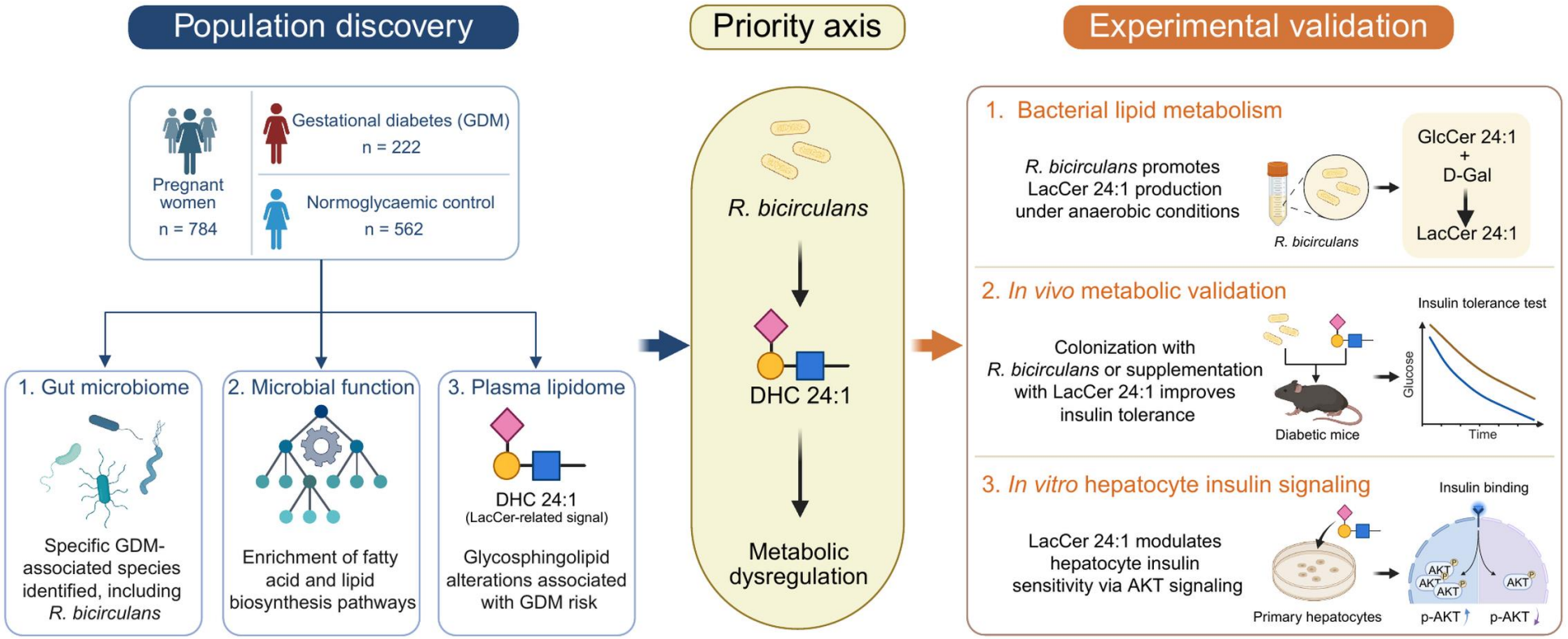


Combined Scores and GDM Risk

		MRS			Relative excess risk due to interaction
		Low	High	Total	
LRS	Low	Ref.	1.29 (0.61, 2.74)	Ref.	11.83 (3.93, 19.73)
	High	5.64 (3.02, 11.03)	19.19 (10.63, 36.81)	8.24 (5.51, 12.61)	
GRS	Low	Ref.	2.76 (1.66, 4.66)	Ref.	1.36 (-0.30, 3.02)
	High	1.09 (0.59, 1.98)	4.44 (2.68, 7.53)	1.39 (0.99, 1.96)	
	Total	Ref.	2.74 (1.96, 3.86)	-	-

Figure 6D-E. Microbial, lipid, and genetic risk scores and their joint associations with later GDM.

Summary



- GDM-related gut microbial and lipidomic changes were already evident in early pregnancy, before clinical diagnosis.
- Population and experimental findings support a link between microbial glycosphingolipid metabolism and host insulin responses.
- Microbiome and lipidome data may improve early GDM risk stratification, pending external validation.

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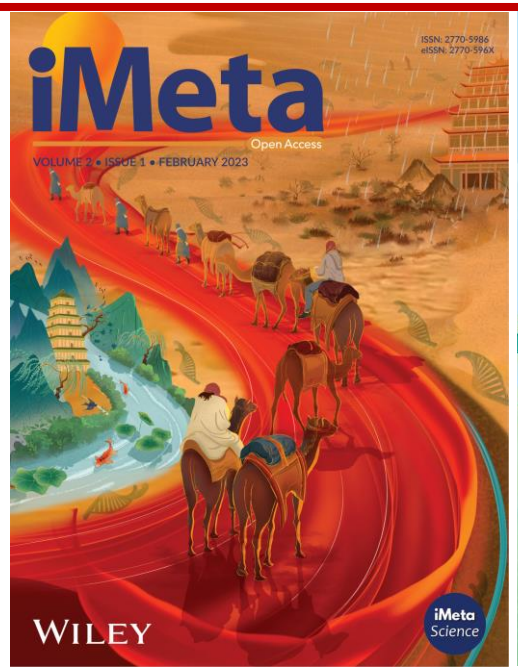

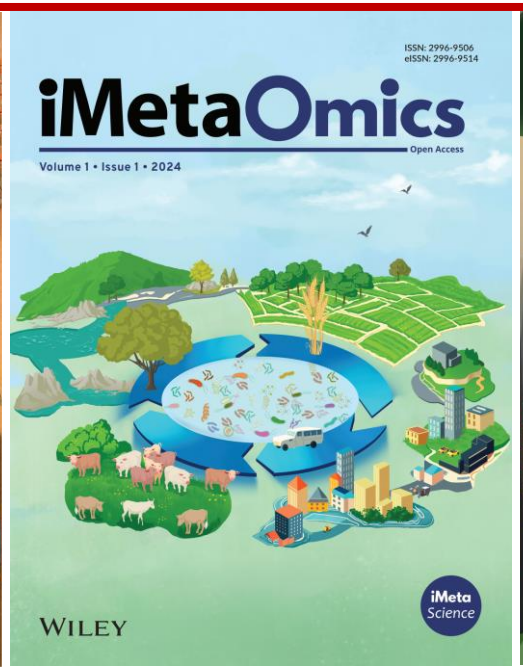

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