Distinct microbial and metabolic shifts characterize acute coronary syndrome and recovery

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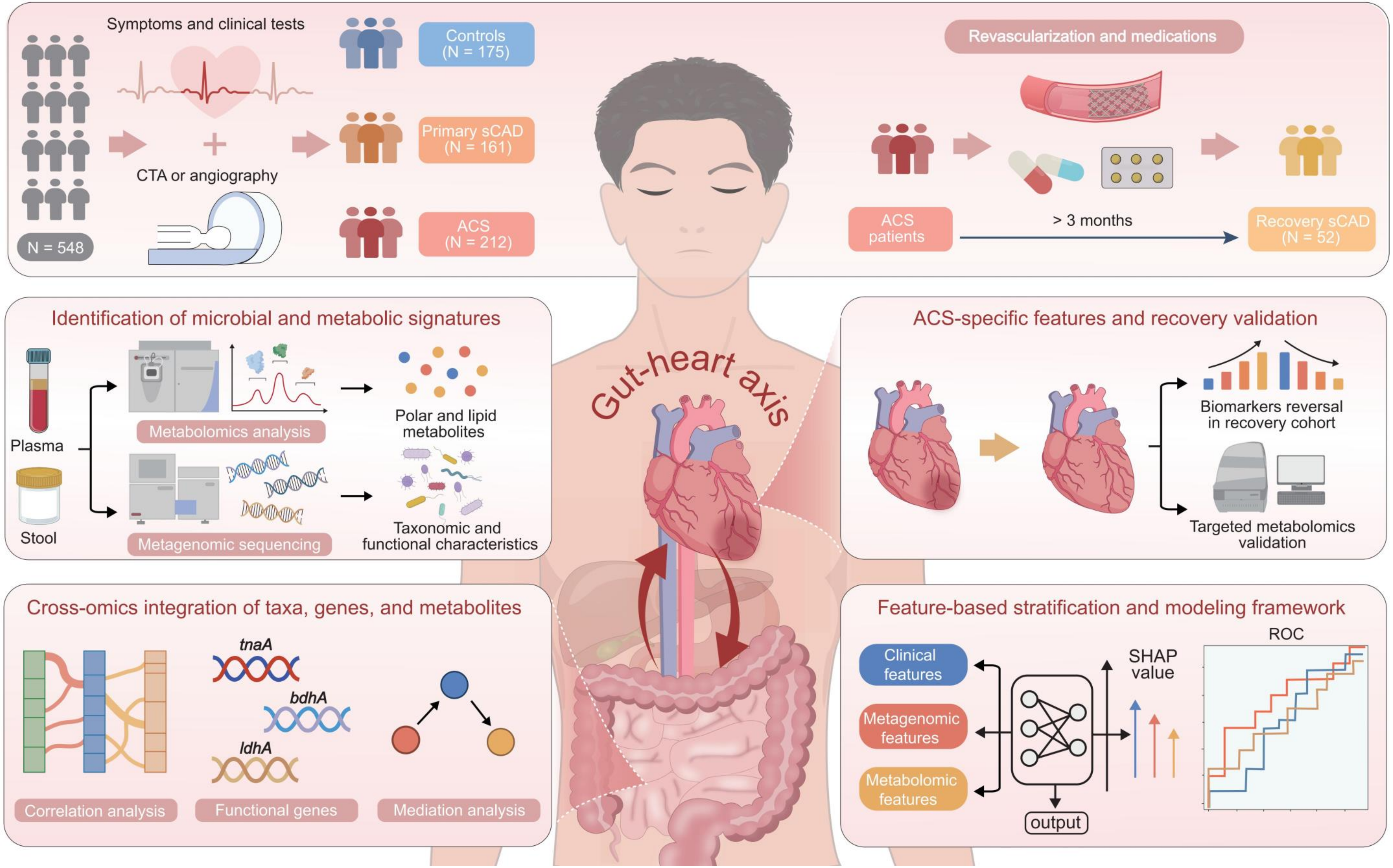
Introduction



Symptoms and clinical tests

+

CTA or angiography

N = 548

Controls (N = 175)

Primary sCAD (N = 161)

ACS (N = 212)

Revascularization and medications

ACS patients

> 3 months

Recovery sCAD (N = 52)

Gut-heart axis

Identification of microbial and metabolic signatures

Plasma

Stool

Metabolomics analysis

Polar and lipid metabolites

Metagenomic sequencing

Taxonomic and functional characteristics

ACS-specific features and recovery validation

Biomarkers reversal in recovery cohort

Targeted metabolomics validation

Cross-omics integration of taxa, genes, and metabolites

tnaA

bdhA

ldhA

Correlation analysis

Functional genes

Mediation analysis

Feature-based stratification and modeling framework

Clinical features

Metagenomic features

Metabolomic features

output

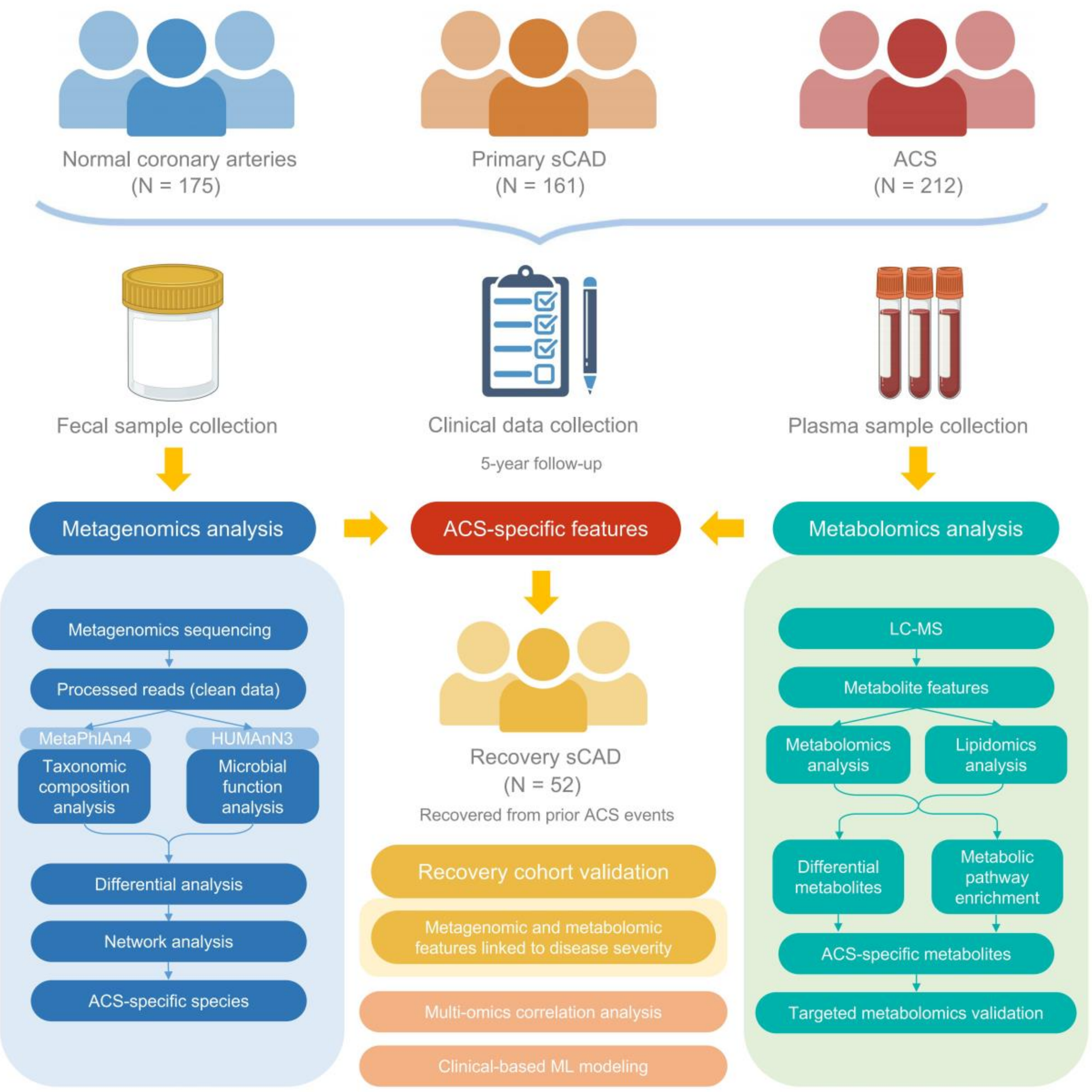
SHAP value

ROC

Highlights

- Gut microbiota and circulating metabolites display stage-specific alterations across NCA, sCAD, and ACS, underscoring the gut–heart axis in CAD progression.
- ACS-specific microbial and metabolic signatures were identified and validated in a recovery cohort, demonstrating partially reversible, stage-specific shifts.
- Multi-omics machine learning models accurately stratified CAD subtypes, surpassing the predictive power of clinical risk factors alone.

Study design and baseline characteristics of the cohort



Normal coronary arteries
(N = 175)

Primary sCAD
(N = 161)

ACS
(N = 212)

Fecal sample collection

Clinical data collection

5-year follow-up

Plasma sample collection

Metagenomics analysis

ACS-specific features

Metabolomics analysis

Metagenomics sequencing

Processed reads (clean data)

MetaPhlAn4

HUMAnN3

Taxonomic composition analysis

Microbial function analysis

Differential analysis

Network analysis

ACS-specific species

Recovery sCAD
(N = 52)

Recovered from prior ACS events

Recovery cohort validation

Metagenomic and metabolomic features linked to disease severity

Multi-omics correlation analysis

Clinical-based ML modeling

LC-MS

Metabolite features

Metabolomics analysis

Lipidomics analysis

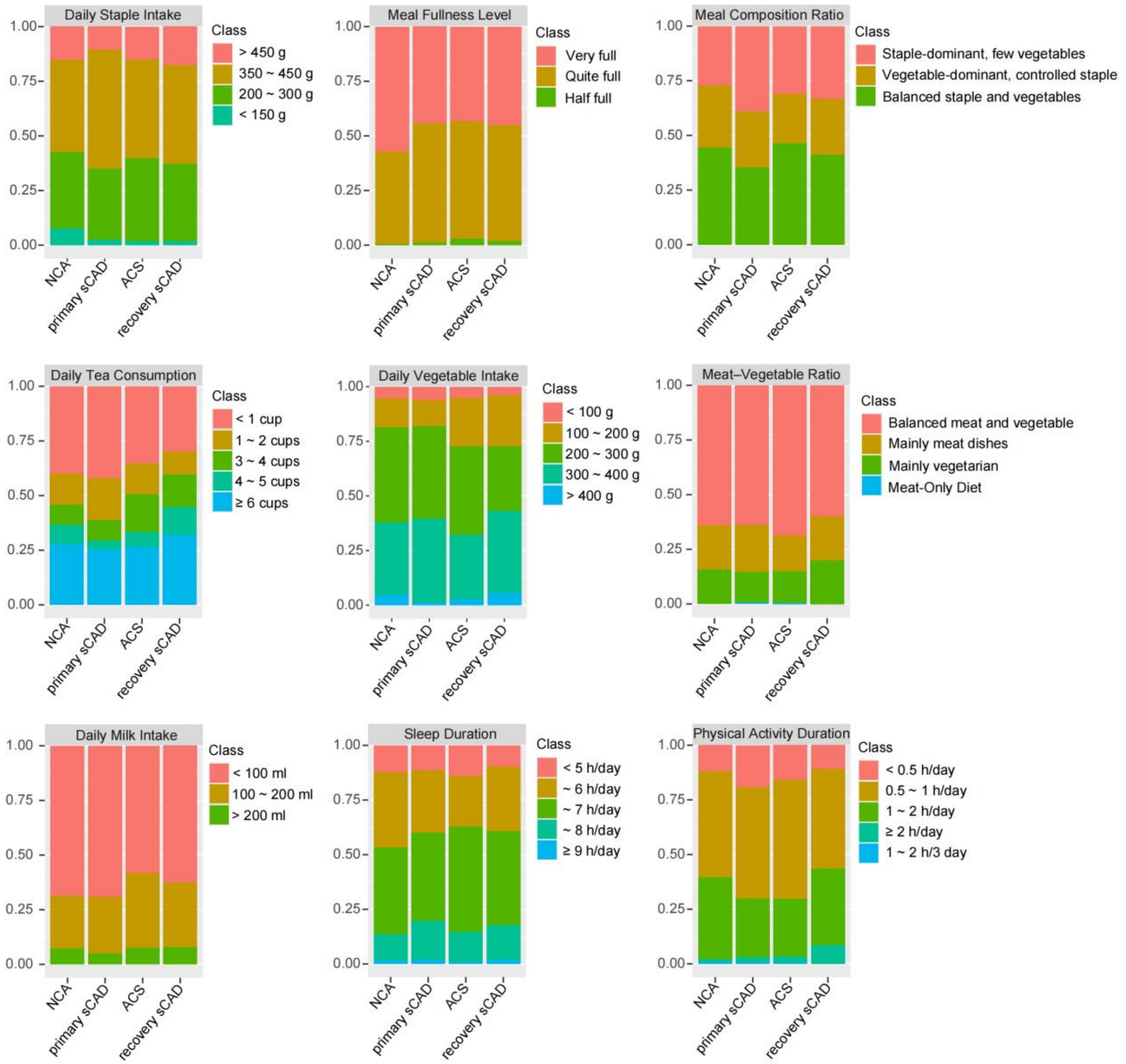
Differential metabolites

Metabolic pathway enrichment

ACS-specific metabolites

Targeted metabolomics validation

Figure 1. Overview of study workflow and participant cohort.



No significant intergroup differences in lifestyle or diet were observed.

Overall gut microbiome profiles in CAD

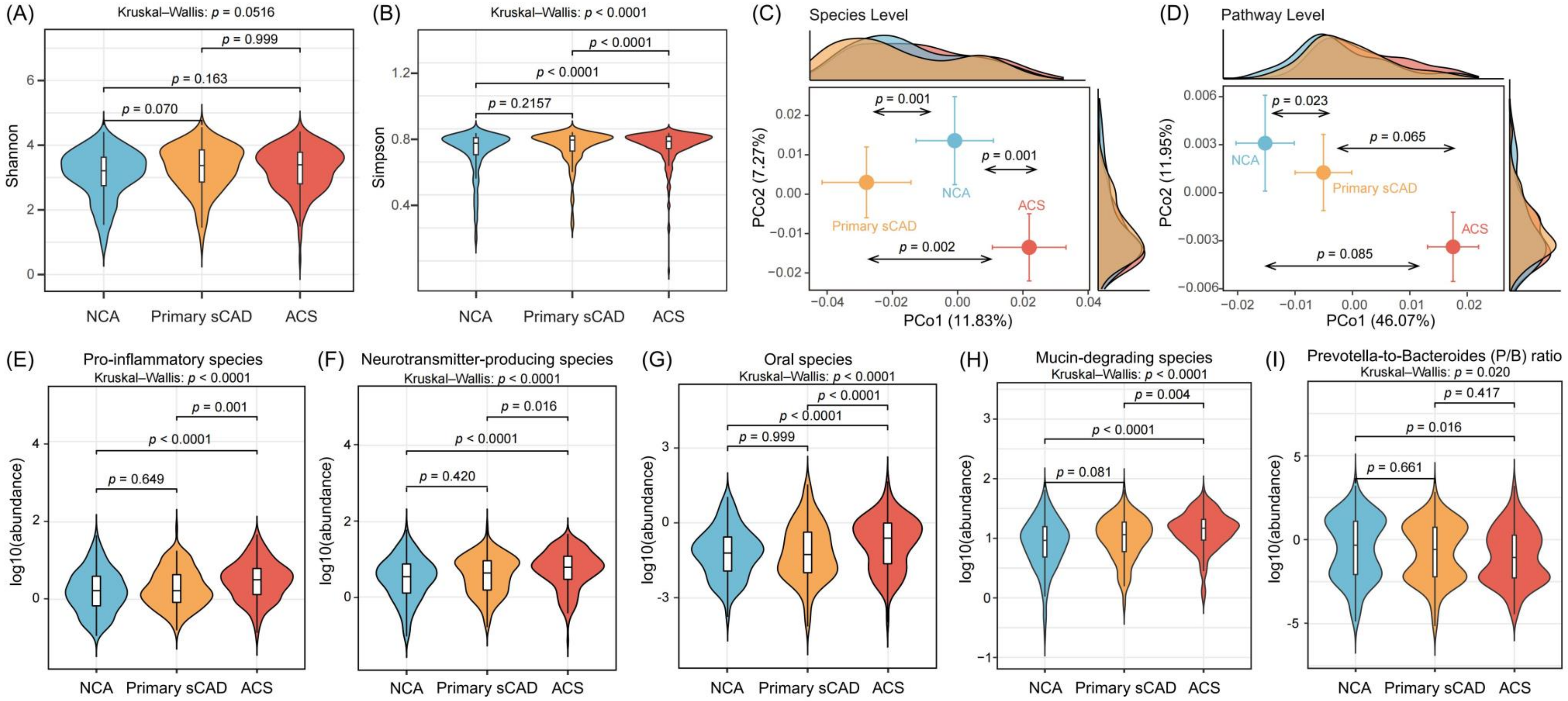


Figure 2. Comprehensive analysis of gut microbiota changes from NCA to ACS

- **Diversity:** No significant difference in Shannon diversity; ACS patients had significantly higher Simpson diversity.
- **Community structure:** Significant separation among three groups at the species level; at the pathway level, only NCA vs sCAD was significant, while comparisons involving ACS did not reach significance.
- **Functional taxa:** ACS enriched in pro-inflammatory, neurotransmitter-producing, oral-origin, and mucin-degrading species; P/B ratio decreased.

Overall gut microbiome profiles in CAD

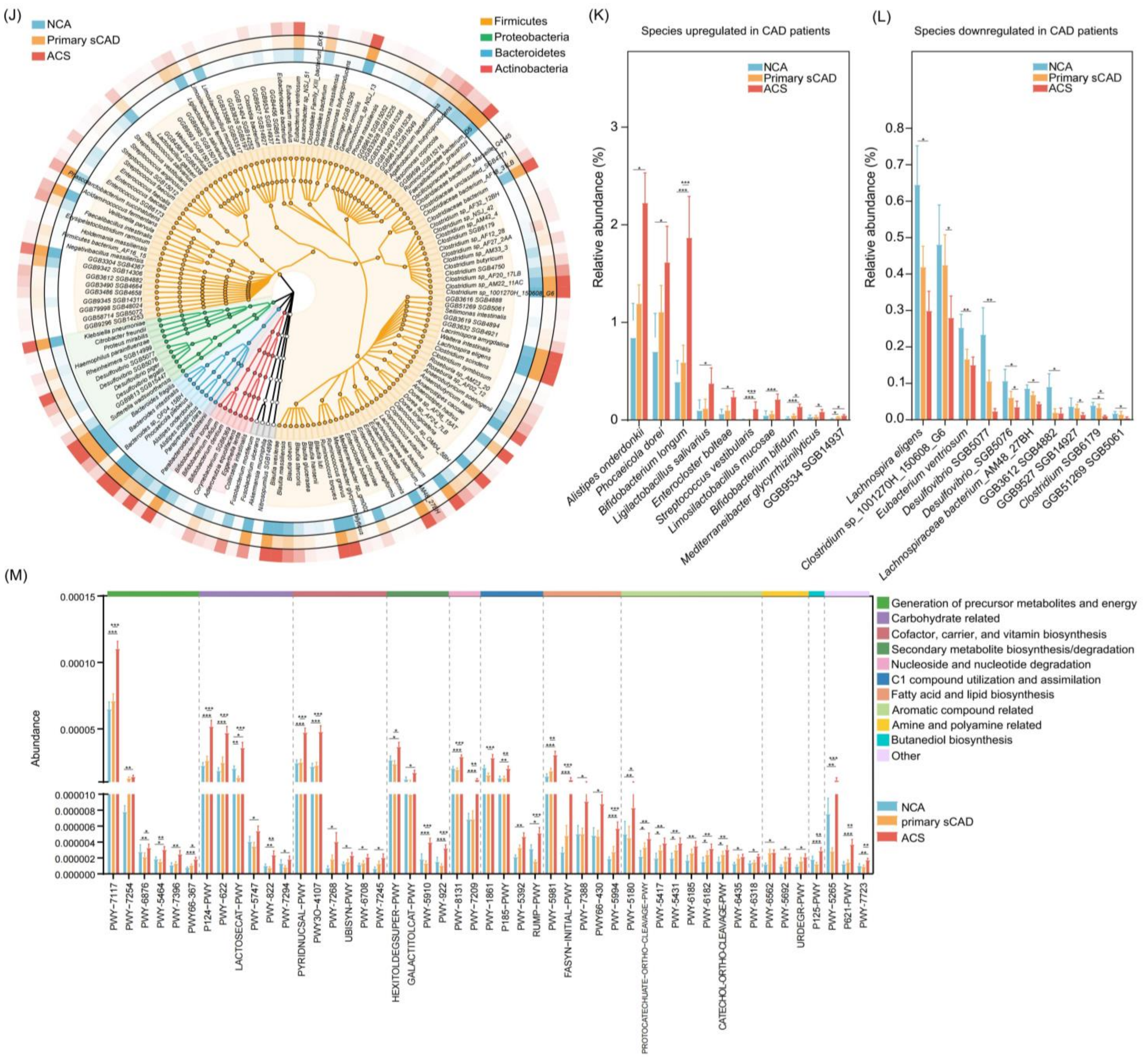


Figure 2. Comprehensive analysis of gut microbiota changes from NCA to ACS

- **Characteristic shifts:** Pro-inflammatory taxa such as *Streptococcus* spp. increased, while barrier-supporting/anti-inflammatory taxa including *Lachnospiraceae* spp. and *Clostridium* spp. decreased.
- **Pathways:** ACS enriched in fatty acid and ketogenesis, phenol and formaldehyde metabolism, and mevalonate-related pathways.

Plasma metabolomic and lipidomic profiles in CAD

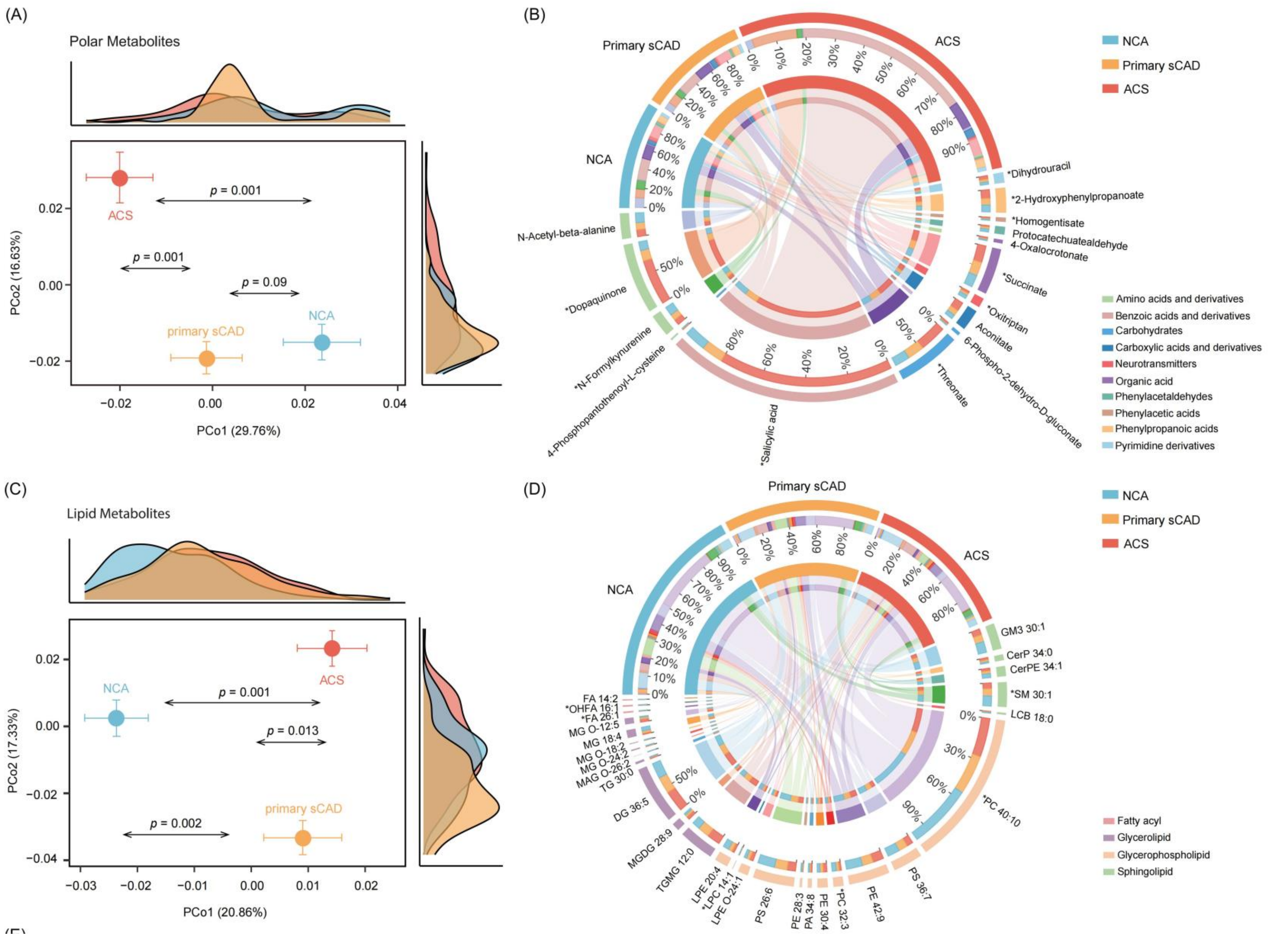


Figure 3. Metabolomic and lipidomic profiles associated with CAD progression

- **Metabolite shifts:** Clear separation among NCA, sCAD, and ACS based on metabolite profiles.
- **ACS features:** Elevated organic acids, carboxylic acids, phenylpropanoic derivatives; reduced amino acids and neurotransmitter-related metabolites.
- **Lipid changes:** Increased triglycerides and sphingolipids; decreased phospholipids and fatty acids.

Plasma metabolomic and lipidomic profiles in CAD

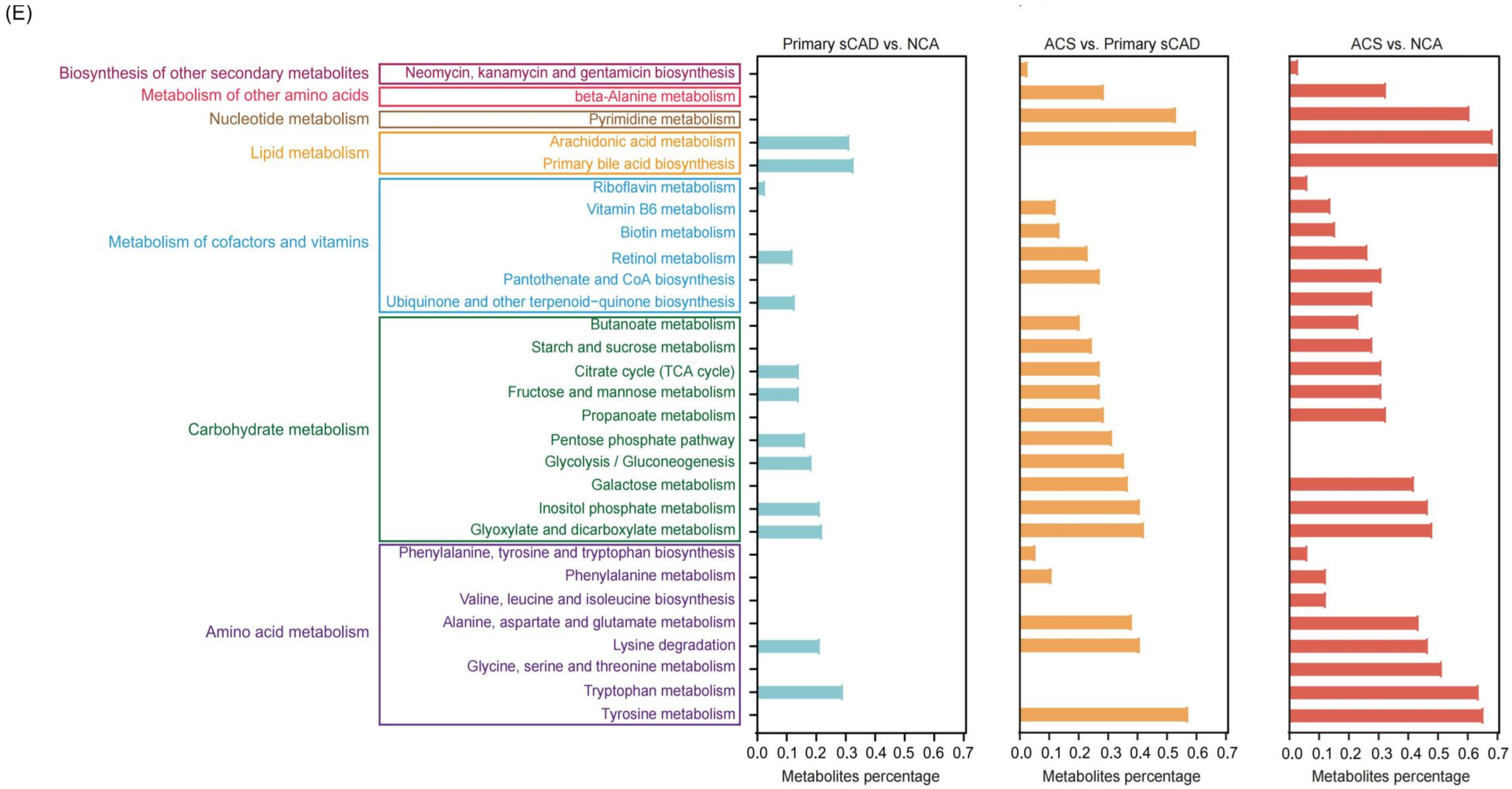


Figure 3. Metabolomic and lipidomic profiles associated with CAD progression

- **Pathway enrichment:** ACS enriched in amino acid and carbohydrate metabolism pathways.

ACS-specific microbial and metabolic characteristics

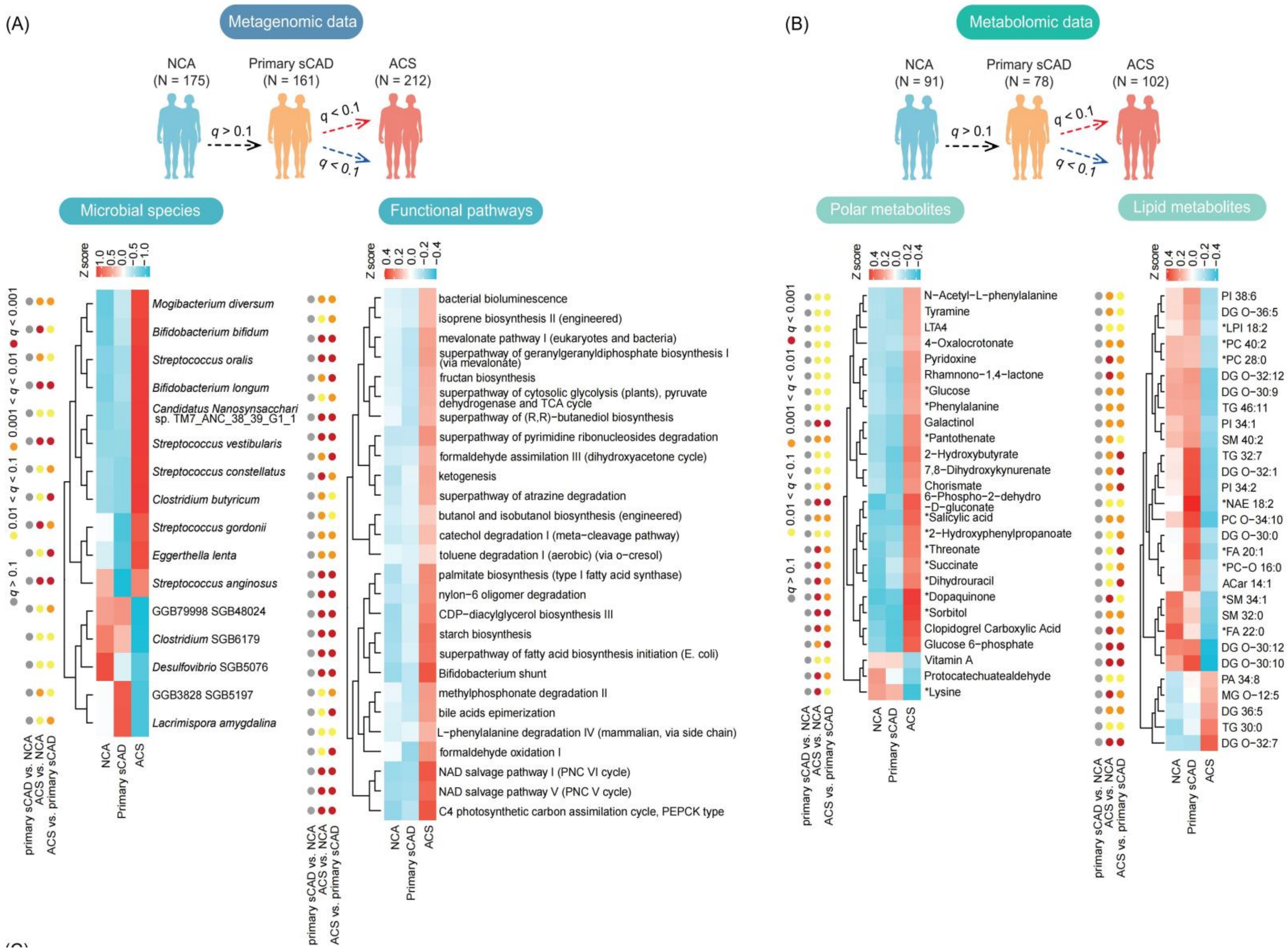


Figure 4. ACS-specific microbial and metabolic characteristics

- **Microbial taxa:** Elevated *Streptococcus* spp., *Bifidobacterium* spp.; decreased *Clostridium* spp. and *Desulfovibrio* spp.
- **Pathways:** Enrichment of ketogenesis, fatty acid metabolism, and bile acid biosynthesis in ACS.
- **Metabolites:** Increased 2-hydroxybutyrate, phenylalanine and derivatives, succinate; decreased lysine and vitamin A.
- **Lipid profiles:** Elevated diacylglycerols and triglycerides; reduced phospholipids.

ACS-specific microbial and metabolic characteristics

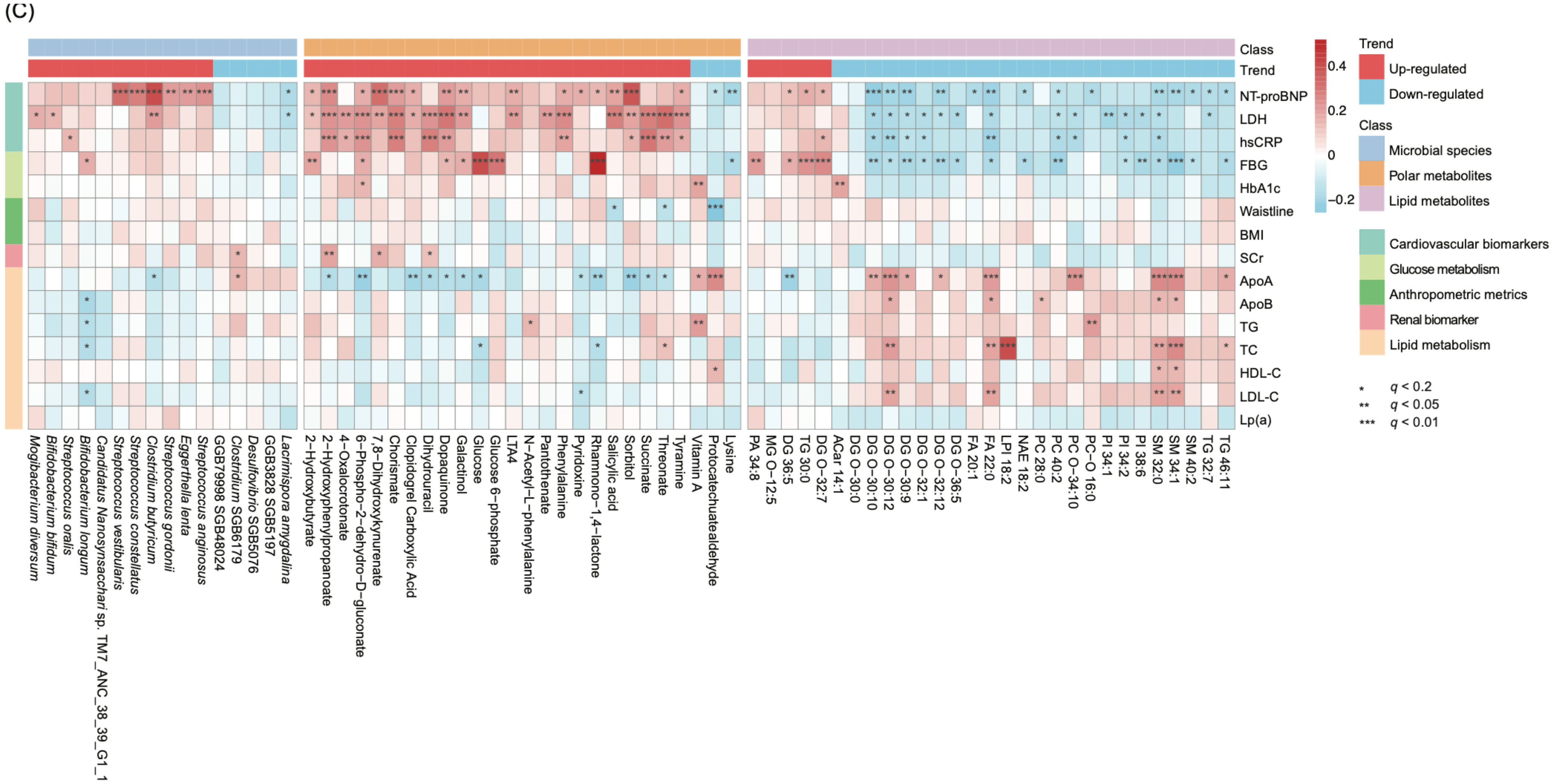


Figure 4. ACS-specific microbial and metabolic characteristics

- **Clinical correlations:** These features strongly correlated with inflammatory and cardiac injury markers such as NT-proBNP and hs-CRP.

Restoration of gut microbiota and metabolites following ACS recovery

- **Study cohort:** 52 patients transitioned from ACS to stable CAD
- **Microbiota shifts:** Recovery patients resembled sCAD and diverged from ACS
- **ACS features reversed:** Pro-inflammatory taxa such as *Streptococcus* spp. decreased

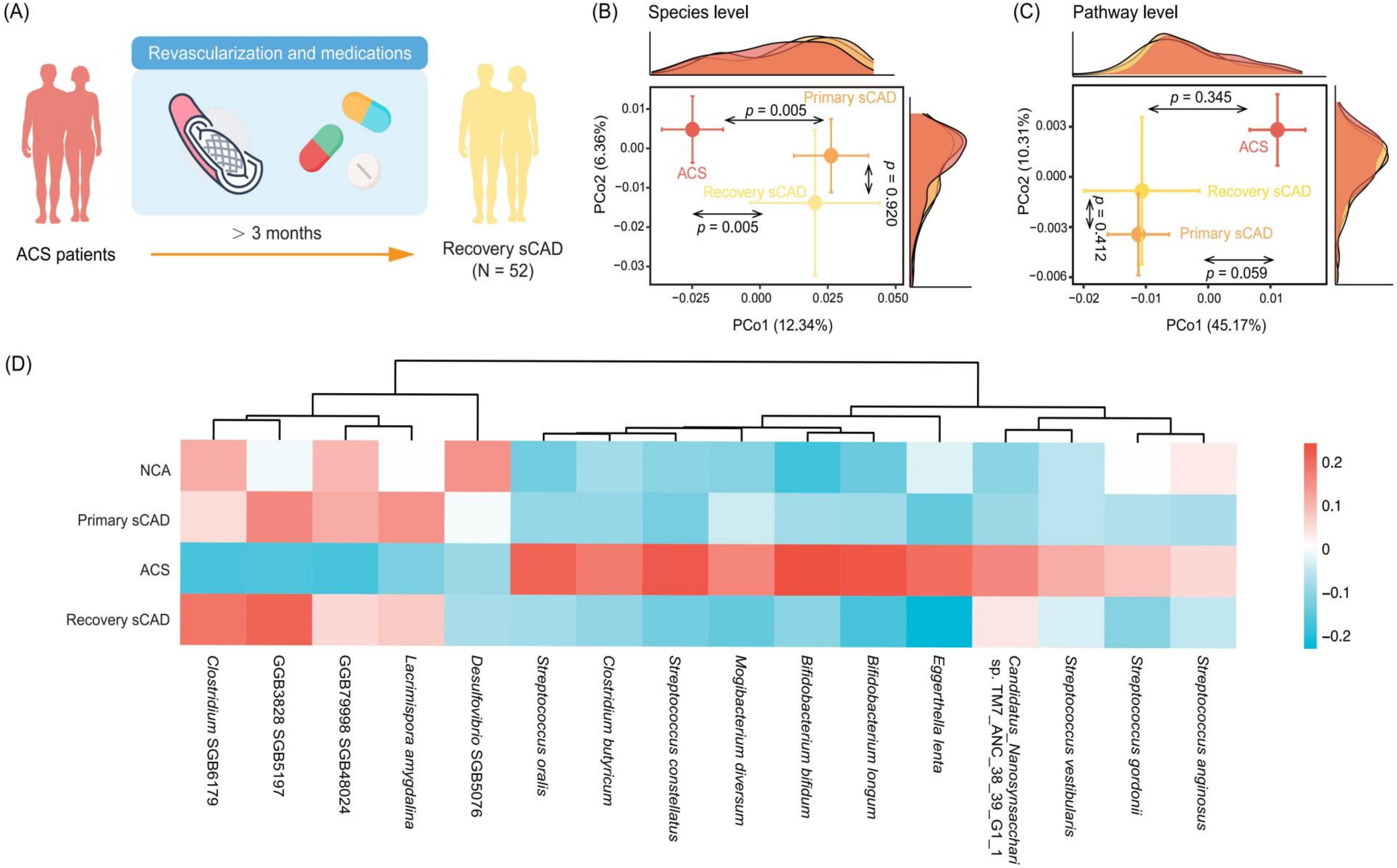


Figure 5. Gut microbiota and metabolite changes during ACS recovery

Restoration of gut microbiota and metabolites following ACS recovery

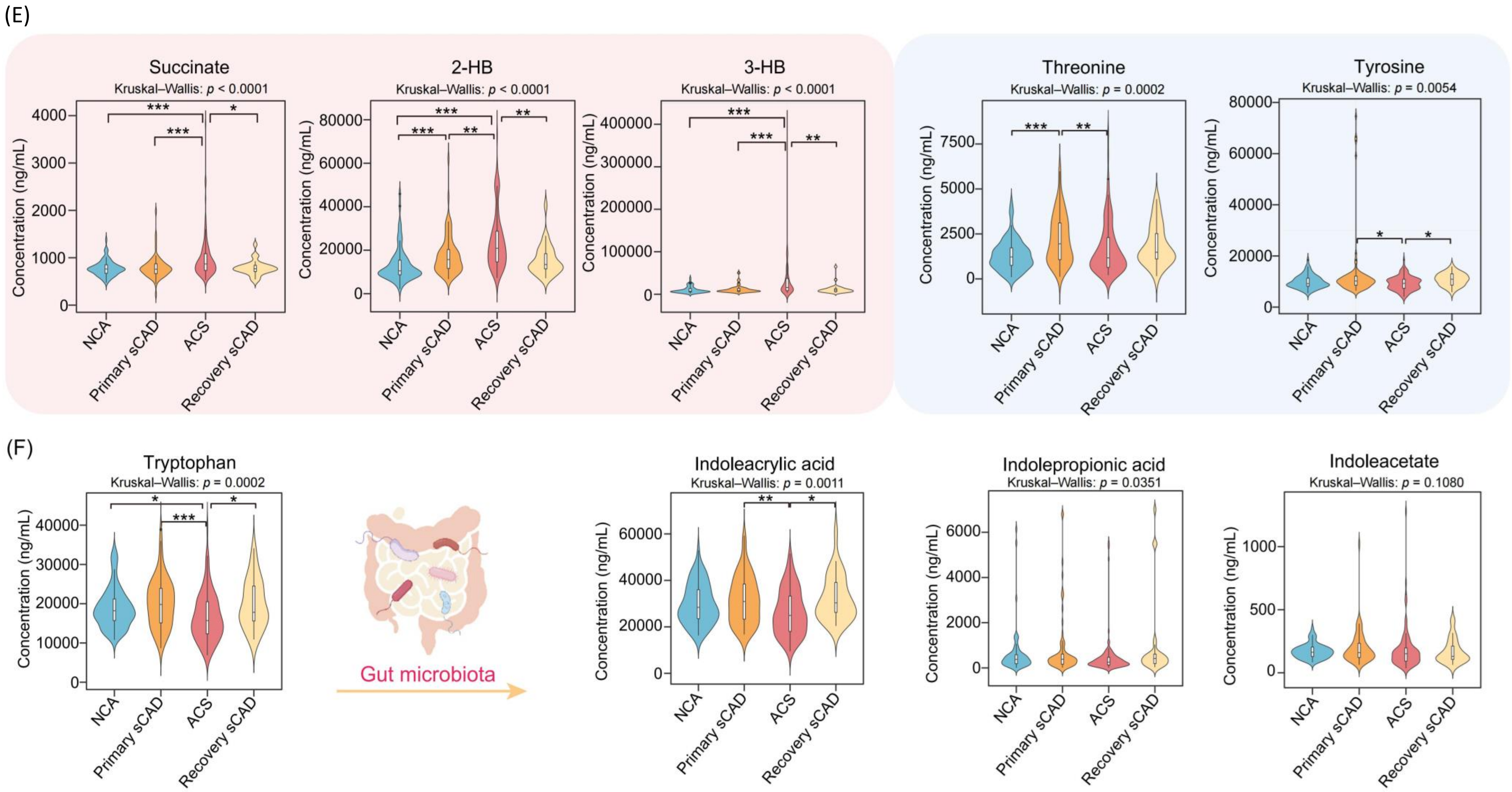


Figure 5. Gut microbiota and metabolite changes during ACS recovery

- **Metabolite trends:** Elevated 2-HB, 3-HB, and succinate in ACS decreased after recovery; amino acids increased
- **Clinical implication:** ACS-related microbial and metabolic features are partially reversible, highlighting their potential as recovery biomarkers

Multi-omics correlation analysis reveals the microbiota-metabolite-pathway links in ACS pathophysiology

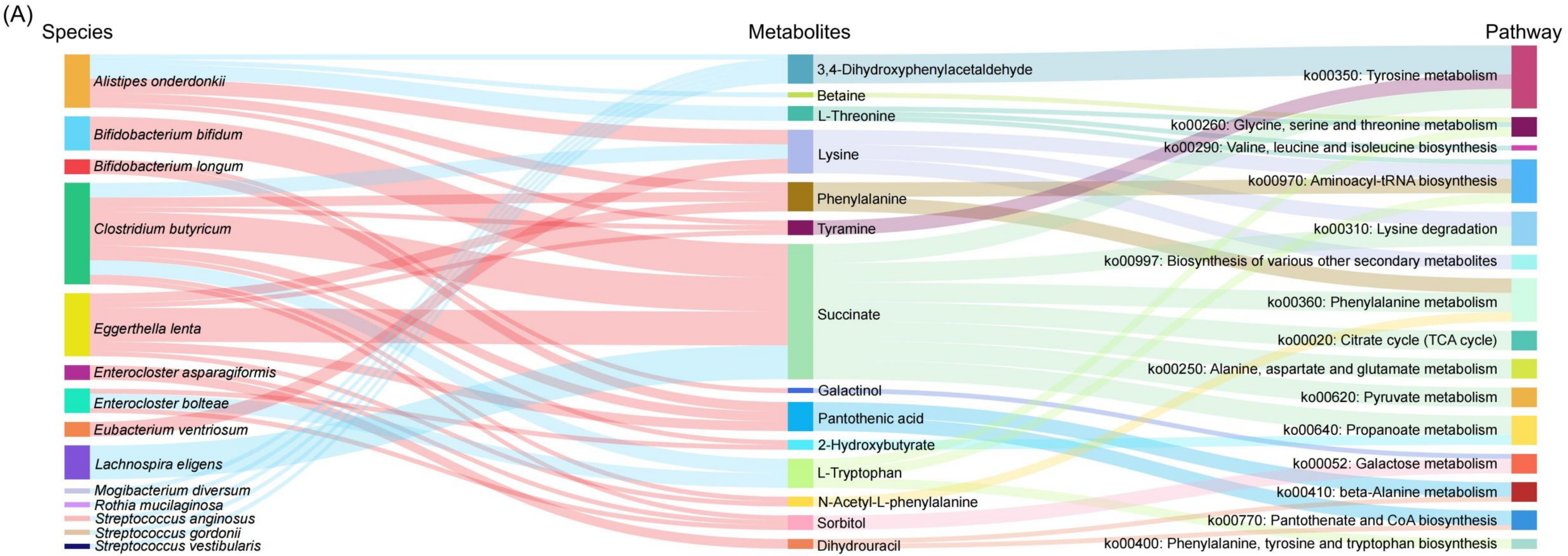


Figure 6. Multi-omics integration reveals microbiota–metabolite interplay in ACS

- **Method:** MetOrigin was applied to integrate gut microbiota with circulating metabolites
- **Key metabolites:** Elevated 2-HB, 3-HB, and succinate positively correlated with multiple microbes
- **Amino acid metabolism:** Reduced tryptophan showed negative associations with specific taxa

Multi-omics correlation analysis reveals the microbiota-metabolite-pathway links in ACS pathophysiology

- **Functional genes:** ACS enriched in microbial genes for 3-HB, succinate, and tryptophan metabolism
- **Mechanistic insight:** Gut microbes may contribute to ACS through metabolic pathway regulation

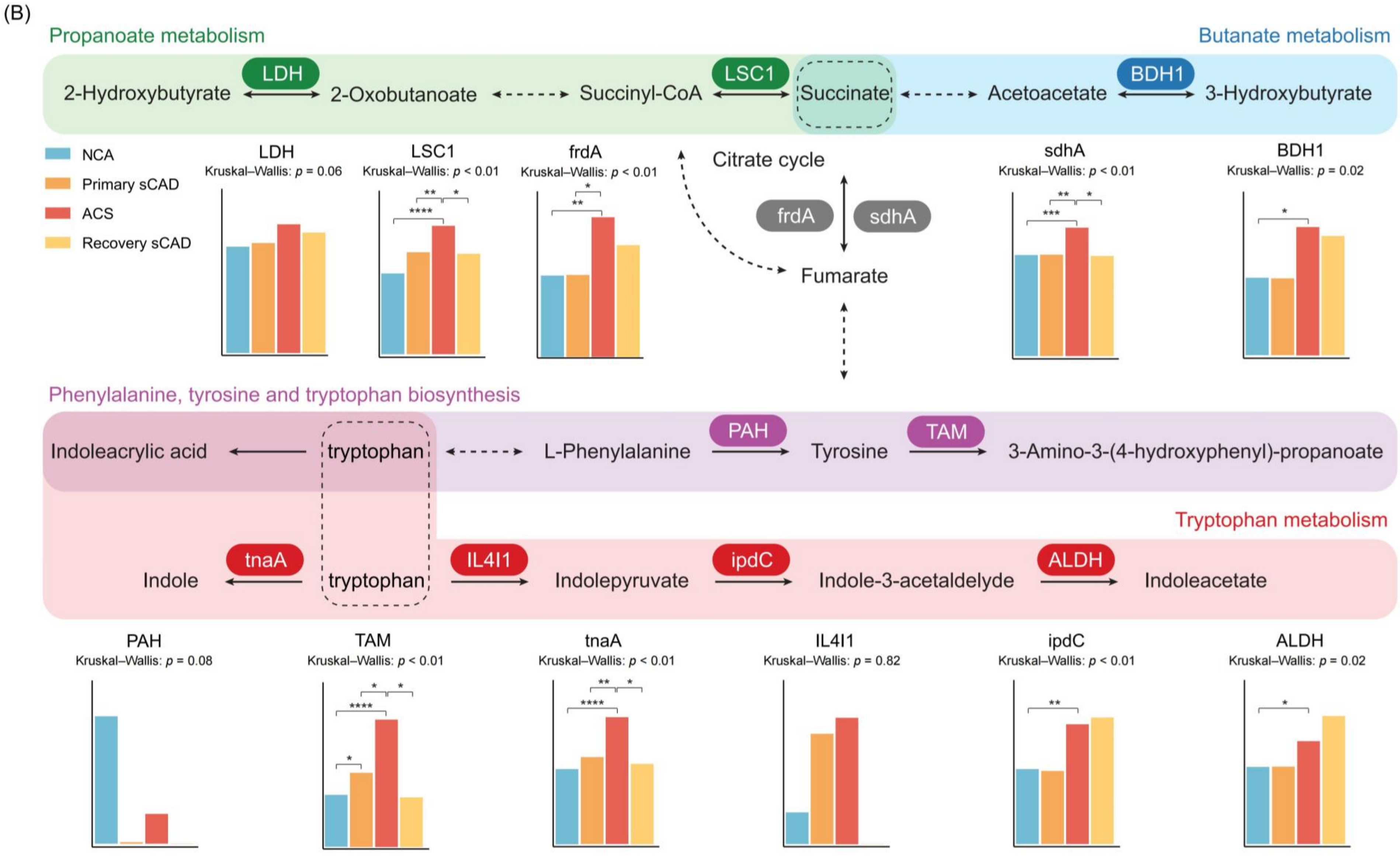
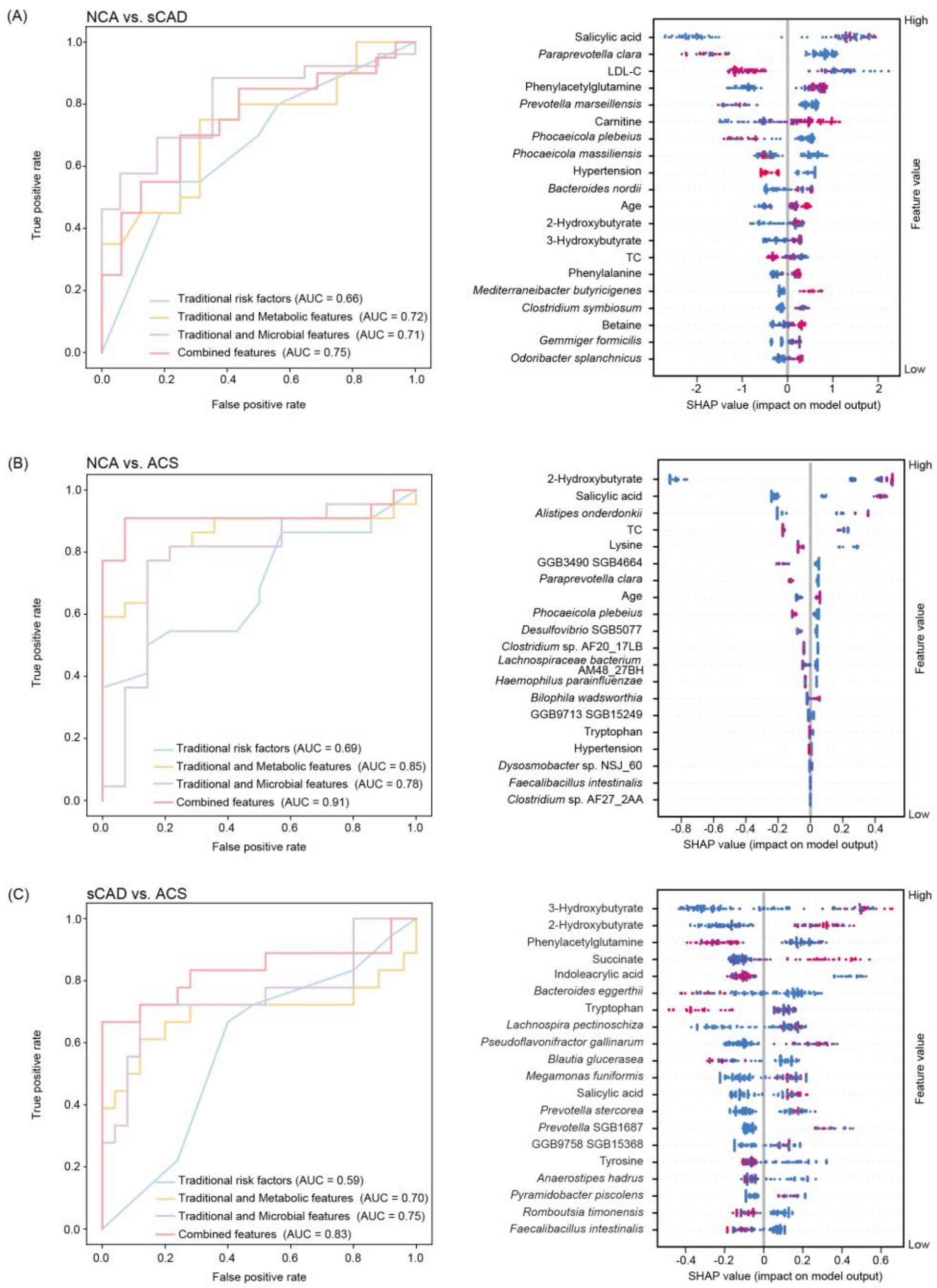


Figure 6. Multi-omics integration reveals microbiota–metabolite interplay in ACS

Integrating clinical, microbial, and metabolic features to distinguish different CAD stages using machine learning models



- **Method:** LightGBM machine learning framework
- **Findings:**

Clinical markers alone showed limited performance (AUC < 0.7)

Adding metabolites and microbial features greatly improved discrimination

- **Performance:**

NCA vs sCAD: AUC = 0.75

NCA vs ACS: AUC = 0.91

sCAD vs ACS: AUC = 0.83

- **Conclusion:** Multi-omics integration outperformed traditional clinical markers

Figure 7. Multi-omics models distinguish CAD stages

Summary

- ❑ ACS patients exhibit stage-specific alterations in gut microbiota and metabolites
- ❑ Inflammation-related microbes and metabolites play an important role in ACS
- ❑ Recovery patients display partial reversal of ACS-specific features
- ❑ Microbial and metabolic features hold promise as biomarkers for risk assessment and therapeutic targets

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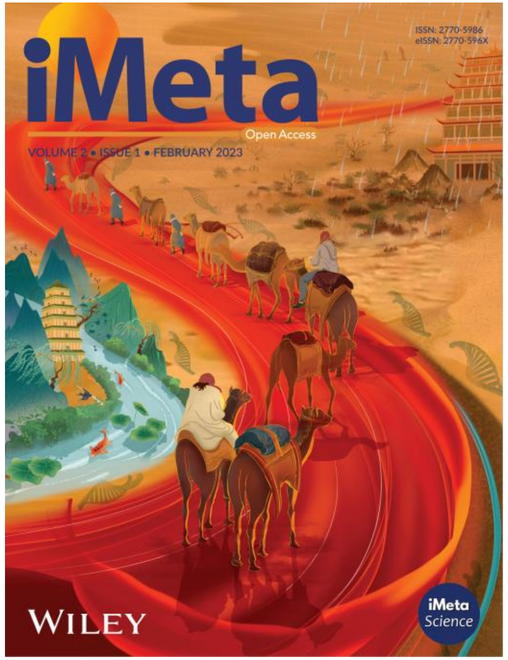

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