Longitudinal profiling of the microbiome at four body sites reveals core stability and individualised dynamics during health and disease

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1. Abstract

This study investigates the dynamic interplay between the human microbiome and host health, focusing on prediabetes. It analyzes microbial composition, temporal dynamics, and their associations with multi-omics, immune markers, and clinical profiles. By examining microbiomes from four body sites in 86 participants over six years, it addresses limitations of previous studies, such as a lack of longitudinal data, single-site focus, and insufficient integration of microbiome data with host clinical and molecular profiles. Using data from longitudinal initiatives like Integrative Human Microbiome Project and Integrative Personal Omics Profiling, it allows the study to investigate well-characterized human longitudinal cohorts. Individual specific and commonly shared bacterial taxa were identified to show greater stability with microbiome dynamics also correlating across body sites, suggestion systemic dynamics influenced by host microbial environment interactions. Insulin resistant individuals showed altered microbial stability and associations among microbiome, molecular markers, and clinical features suggesting their disrupt interaction in metabolic diseases. Therefore, the study offers comprehensive views of multisite microbial dynamics and their relationship with host health and disease

2. Introduction

Background

The etiology and pathogenesis of insulin resistance and T2DM have been closely linked to the human microbiome.

Research Question

While prior studies on the microbiome and glucose homeostasis have been informative, they exhibit certain limitations.

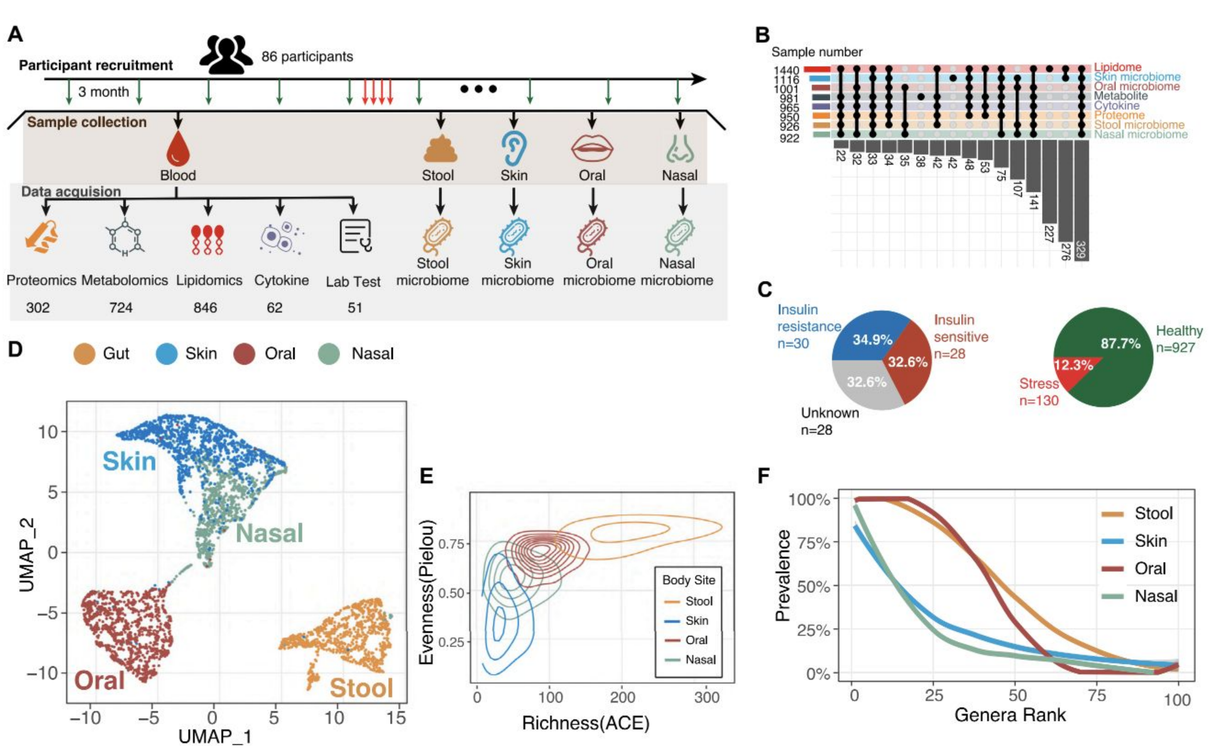
This study aimed to examine the relationships between multi-site microbiomes and host health in the context of prediabetes, through characterizing the microbiome collected from four body sites in 86 adults for over 6 years and examining their associations with host omics and clinical characteristics.

Hypothesis

The study hypothesizes that insulin resistance disrupts the systemic coordination of microbiomes across multiple sites contributing to metabolic dysfunction and progression from diabetes to T2DM.

3. Methods & Materials

Study design: Stool, skin, oral, and nasal microbiome from a human cohort of 86 participants were analysed for up to 6 years.The participants were divided into two groups based on their glucose control assessments: insulin-sensitive (IS) (n=28) and insulin-resistant (IR) (n=30) and unknown insulin state (n=28). Insulin sensitivity was assessed using established measures like oral glucose tolerance test and steady-state plasma glucose measurements.



Methods:

- 16S rRNA Sequencing: This method was used to profile the microbial taxa present in the samples, offering a deep dive into the community composition across all four body sites.
- Proteomics and Metabolomics: These techniques provided insights into the protein and metabolite profiles linked to the microbiomes, helping to connect microbial activity with broader metabolic processes.
- Lipidomics: We examined the lipid pathways in the host to understand how these interact with microbiomes, particularly in relation to metabolic and immune health.
- Cytokine Analysis: This was done to assess inflammatory markers, as inflammation plays a central role in insulin resistance and metabolic dysfunction.

4. Results

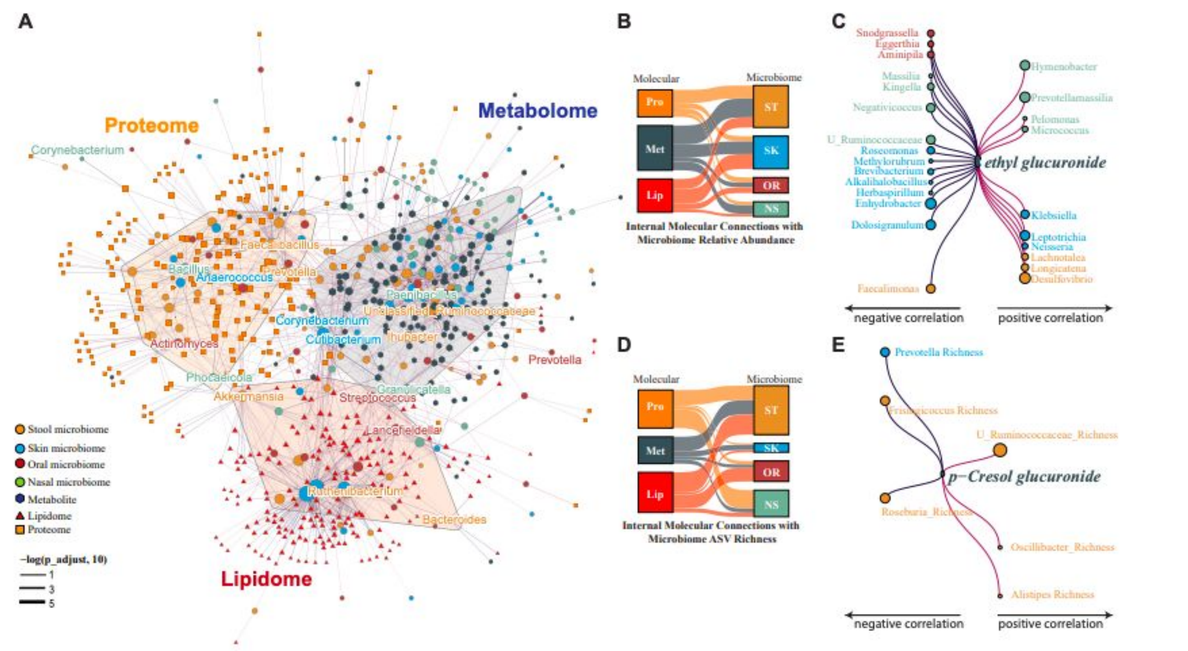


Figure 5. Interactions between plasma metabolites, lipids, proteomics, and microbiome over time

Figure 5A: Interaction network categorized by molecular composition (lipidome, proteome, metabolome) rather than body site.
Figure 5B: Consistent taxa-molecule interactions across body sites, showing systemic coordination.
Figure 5C: Insulin resistance reduces the complexity of stool microbiome-host interactions, highlighting metabolic disruption.

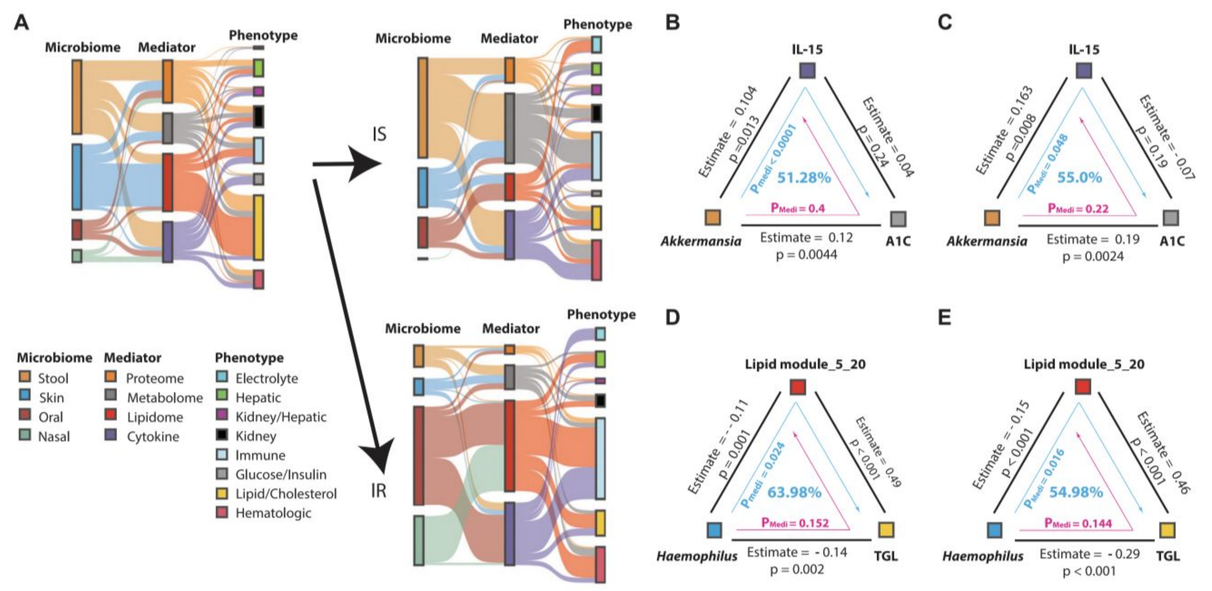
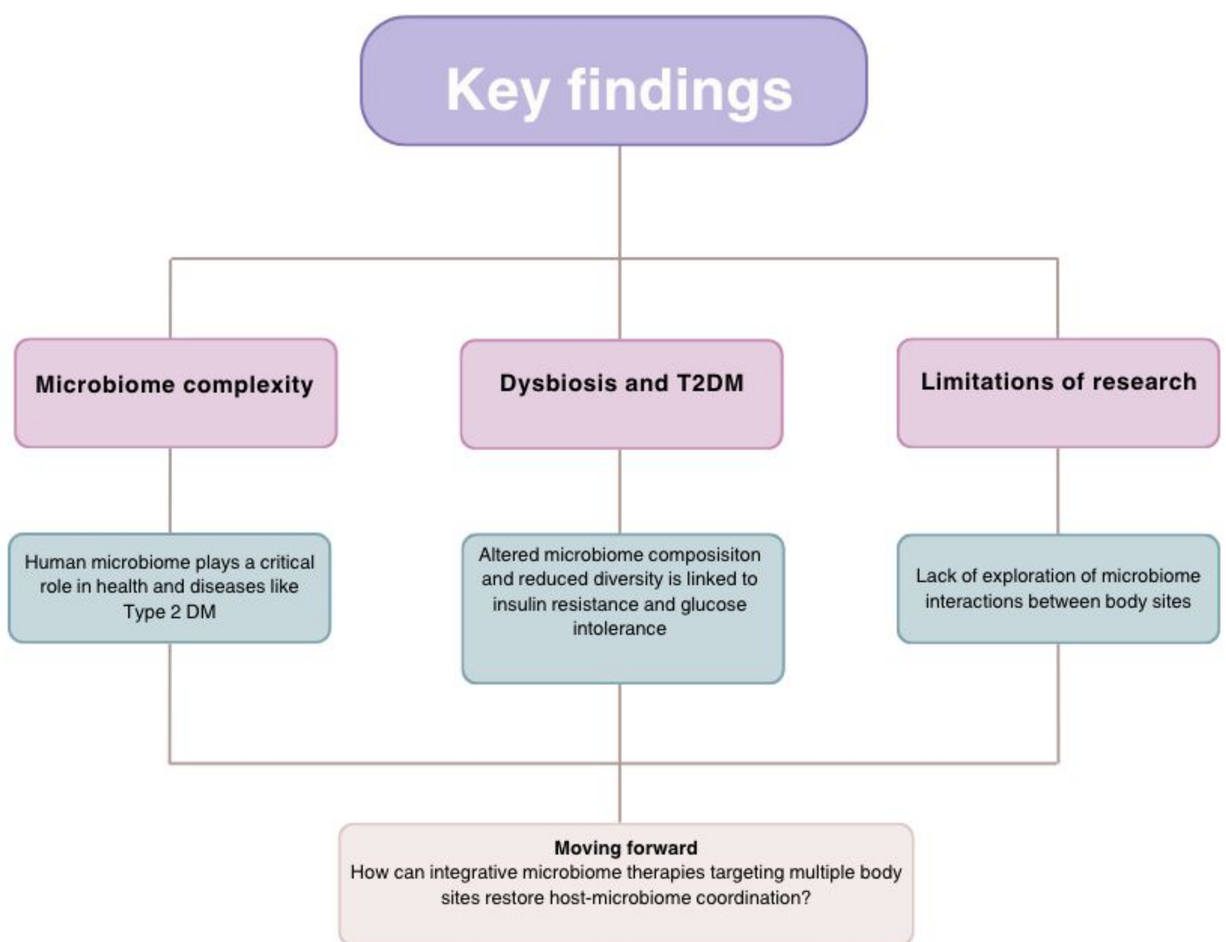


Figure 6. Causal inference decodes microbiome-driven phenotypic dynamics mediated by internal molecules and cytokines

Figure 6A: Stool microbiome mediates HbA1c regulation via cytokines in insulin-sensitive individuals; disrupted in insulin resistance.
Figure 6B: *Akkermansia* mediates HbA1c reductions via anti-inflammatory cytokines, impaired in insulin resistance.
Figure 6C: Stool and skin microbiomes influence plasma triglycerides; disrupted in insulin resistance.

5. Discussion



6. Conclusion

The present study demonstrates that insulin resistance is a key factor in disrupting the typical interaction between host and microbiome at different body sites. This affects the host's ability to regulate metabolic and immune functions. The findings provide a foundation for future development of microbiome-based interventions aimed at improving metabolic health.

7. Acknowledgements

We thank all the participants who contributed to this project.