

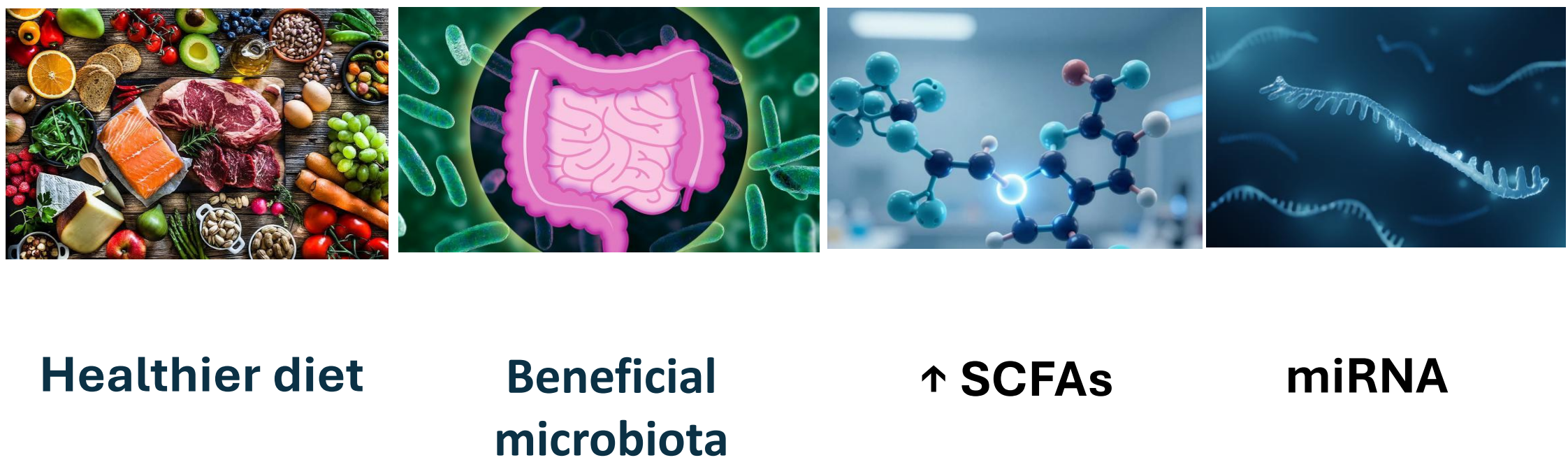
The Gut–Brain Connection: How Diet, Faecal miRNA and Amyloid Status Influence Beneficial Gut Bacteria in Preclinical Alzheimer’s Disease

W.M.A.D. Binosha Fernando¹, Kavisha S. Katuwawala¹, Lahiru S. Perera¹,Sithara Dissanayaka Mudiyansele¹, Stephanie R. Rainey-Smith², Hamid R. Sohrabi², Ralph N. Martins¹, and the AIBL Research Group

¹ Centre of Excellence for Alzheimer’s Disease Research & Care, School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA, Australia, ² Murdoch University, Murdoch, Australia

BACKGROUND & AIM

Alzheimer’s disease (AD) has a prolonged preclinical phase, evidence indicates that alterations in gut microbiota may contribute to early pathological changes. During this stage, gut microbial composition and metabolic activity may be modified by lifestyle factors. Diet influence gut microbial composiiton and metabolic output, while microRNAs (miRNAs) play an important role in host-microbe communication and inflammatory regulation. **However, how diet and miRNA regulation influence beneficial bacterial balance and short-chain fatty acid (SCFA) production, and how these relationships vary across age, sex, APOE genotype, and cerebral amyloid status in cognitively unimpaired individuals, remains unclear.** This study addresses this gap by examining diet-microbiome-miRNA interactions in preclinical AD.



STUDY DESIGN

n = 123 CU adults	Aβ Low vs Aβ High PET amyloid	Adjusted Age • Sex • APOE ε4
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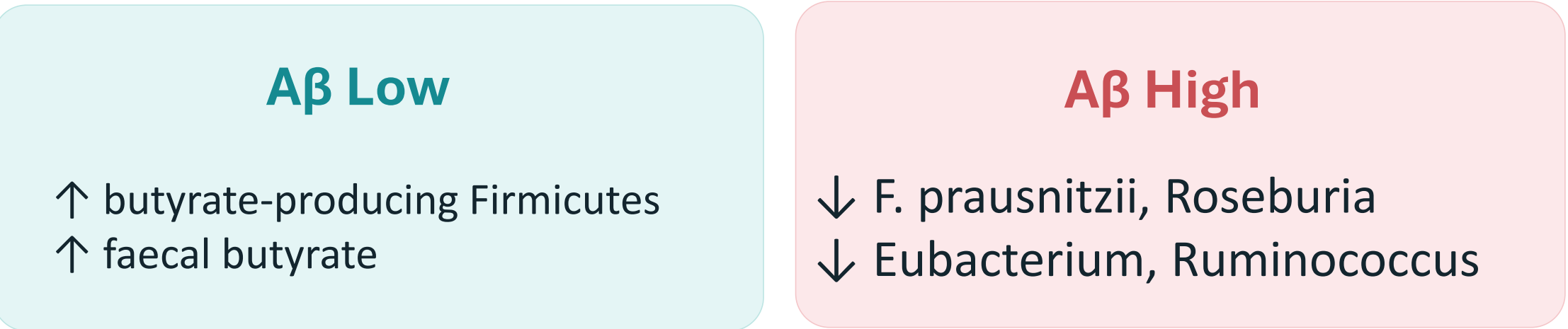
- Stool samples from 123 cognitively unimpaired participants from the Australian Imaging, Biomarkers and Lifestyle Study (AIBL) and the Western Australian Memory Study (WAMS) were analysed.
- Participants were stratified by cerebral amyloid-β (Aβ) status (Aβ Low vs Aβ High).

- Dietary intake was assessed using food frequency questionnaires to derive Mediterranean, DASH, and Western diet adherence scores.
- Shotgun metagenomic sequencing profiled beneficial and SCFA producing bactreas.
- Gas-liquid chromatography quantified faecal SCFAs
- Faecal miRNA expression was assessed using transcriptomic small-RNA profiling.
- Analyses were adjusted for age, sex, and APOE ε4 carrier status.

KEY RESULTS

Age, Sex, and APOE ε4:Gut microbial composition, SCFA profiles, and miRNA expression differed across strata

1 Amyloid status



2 Diet patterns

- Mediterranean + DASH: higher beneficial Firmicutes and butyrate
- Western: lower butyrate and relatively higher acetate

3 Faecal miRNA Associations

miRNA patterns differed by Aβ status and were associated with beneficial Firmicutes abundance and SCFA-related pathways

Examples: hsa-miR-922, hsa-miR-1250-5p, hsa-miR-3620-5p, hsa-miR-6777-5p

INTERPRETATION & CONCLUSION

Main conclusion

- Aβ High participants showed reduced beneficial taxa and altered SCFA profiles, suggesting a less favourable gut metabolic environment
- Lower cerebral amyloid burden was associated with a more favourable gut microbial, metabolic and faecal miRNA profile. Higher amyloid burden was characterised by reduced beneficial bacteria, reduced butyrate and distinct miRNA patterns

Implications

- Diet, microbiome, miRNA interactions may be modifiable early biological pathways
- Faecal profiles may identify gut–brain changes before clinical AD symptoms
- Future longitudinal and mechanistic validation is needed

Core message
Gut microbial metabolism and faecal miRNA may help identify modifiable biological pathways before Alzheimer’s disease symptoms emerge

Acknowledgment

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CONTACT



Binosha Fernando

Edith University, Australia

w.fernando@ecu.edu.au

