

Alterations in short-chain fatty acid composition and intestinal barrier integrity in Alzheimer's disease

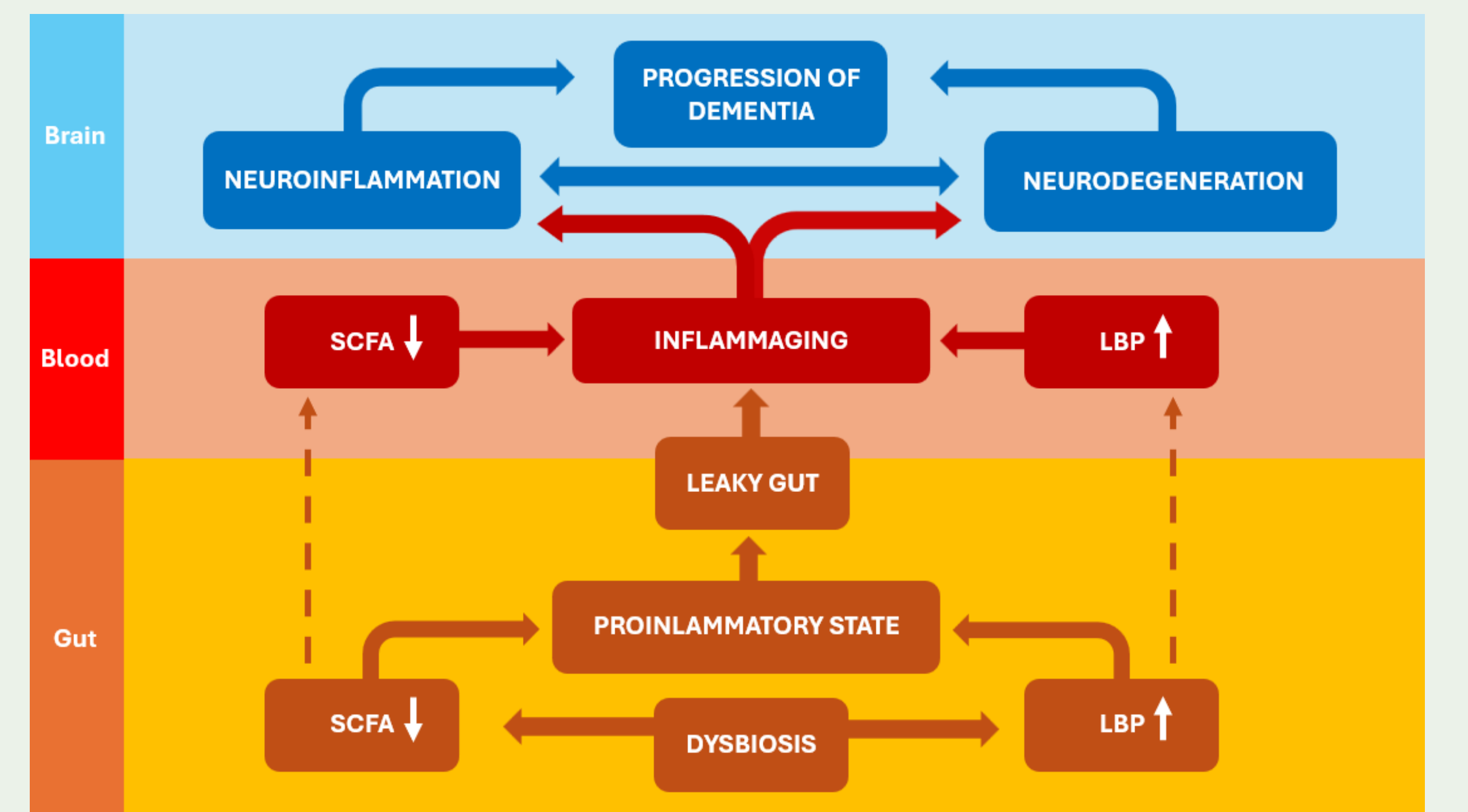
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INTRODUCTION

Evidence suggests that the microbiome plays a role in the development and progression of Alzheimer's disease (AD). Previous studies have shown a decrease in microbiome diversity and a shift towards proinflammatory bacterial taxa in AD. It is assumed that an imbalanced microbiome composition, known as dysbiosis, increases intestinal permeability and promotes low-grade peripheral inflammation, which in turn may contribute to neuroinflammation and amyloid / tau pathology in AD. Bacterial compounds such as lipopolysaccharide (LPS) and short-chain fatty acids (SCFA) can modulate inflammatory pathways and may act as mediators of the gut-brain axis in AD.



AIM

To characterize stage-dependent changes in intestinal and oral microbiome signatures in AD in relation to SCFA composition, markers of intestinal permeability, inflammation and neurodegeneration, thus contributing to our understanding of the gut-brain axis and its role in AD pathophysiology.

METHODS

This study is a subanalysis of our ongoing Microbiome-AD study. As of now, 84 patients with mild cognitive impairment or dementia due to AD, 62 age- and gender-matched healthy controls (HC), and 9 individuals at-risk defined by an apolipoprotein-4 positive genotype have been included. Participants provided stool samples, buccal swabs, and serum. SCFA composition in stool and serum was analyzed by gas chromatography-mass spectrometry, LPS-binding protein serum levels were measured by chemiluminescence immunoassay, and zonulin serum levels were measured by enzyme immunoassay in an external partner laboratory (IMD Berlin). Statistical analysis was performed by one-way analysis of variance using R.

RESULTS

Stool levels of the SCFAs acetate, propionate, and butyrate were significantly decreased in the AD group compared to HC ($p < 0.001$). Serum levels of acetate ($p < 0.05$ [$p < 0.07$ in Tukey's post hoc test]) and propionate ($p < 0.01$) were decreased in AD compared to at-risk individuals, but not to HC, while serum butyrate levels were unchanged between groups.

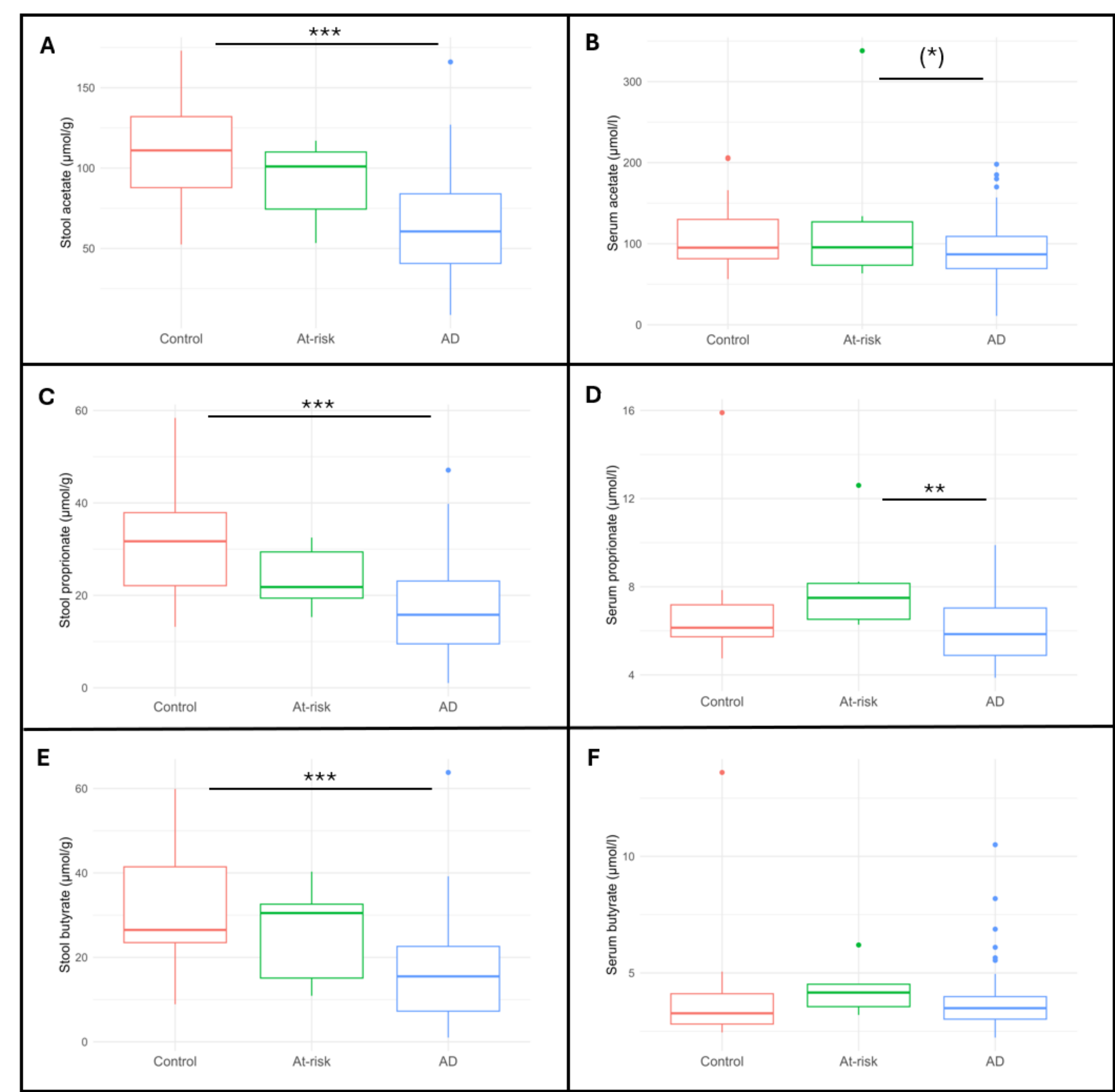


Figure 1: Levels of short-chain fatty acids (SCFA) in stool and serum of Alzheimer's disease (AD) patients compared to at-risk individuals and healthy controls (HC). A) Stool acetate levels were significantly lower in AD compared to HC ($p < 0.001$). B) Serum acetate levels were lower in AD compared to at-risk ($p < 0.05$) but failed to reach significance in Tukey's post hoc test ($p < 0.07$). C) Stool propionate was significantly decreased in AD compared to HC ($p < 0.001$). D) Serum propionate was significantly decreased in AD compared to at-risk individuals ($p < 0.01$). E) Stool butyrate levels were significantly decreased in AD compared to HC ($p < 0.001$). F) Serum butyrate levels were unaltered between groups. N per group (stool): AD = 49, at-risk = 5, HC = 15. N per group (serum): AD = 76, at-risk = 7, HC = 25.

Serum levels of LPS-binding protein (LBP) were not significantly altered between groups. Serum levels of zonulin, a marker of intestinal barrier integrity, were significantly decreased in AD compared to HC ($p < 0.001$).

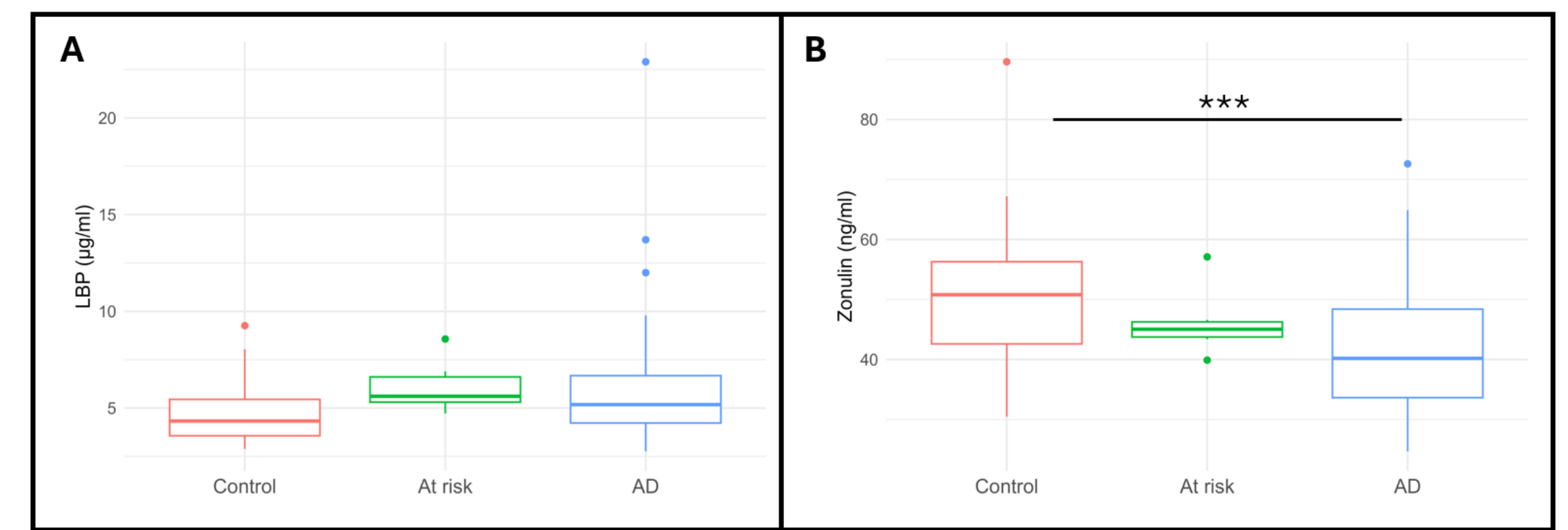


Figure 2: Lipopolysaccharide-binding protein (LBP) and zonulin serum levels in Alzheimer's disease (AD) compared to at-risk individuals and healthy controls (HC). A) No significant difference was found in LBP levels between groups. B) Serum zonulin levels were significantly decreased in AD compared to HC ($p < 0.001$). N per group: AD = 76, at-risk = 7, HC = 25.

CONCLUSION

Our results demonstrate changes in SCFA composition and zonulin levels in AD that are consistent with a proinflammatory microbial state and disruption of the intestinal barrier. Ongoing research will reveal if these alterations are associated with shifts in oral and intestinal microbiome signatures, changes in (neuro-)inflammatory and neurodegenerative markers, and cognitive performance across different stages of AD.

REFERENCES

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