The Effects of a Combined Exercise Intervention on Gut Microbiomes and Systemic Inflammatory Biomarkers in MASLD Patients: A Study Protocol

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ABSTRACT

Introduction:

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent liver disease world-wide. (1,2).
- Disease progression and severity include heightened systemic inflammation, poor diet, inadequate exercise, poor body composition, and unhealthy gut microbiome composition (3,4).
- Although MASLD is due to the lifestyle factors mentioned above, it must be diagnosed in the absence of significant alcohol consumption (3).
- Currently, there are no licensed pharmaceutical agents for the treatment of MASLD, however increasing exercise levels and modifying diet have been shown to reduce disease severity and slow progression - though the underlying mechanisms responsible for these improvements remain unclear (3,4).

Methods:

- **Study 1:** A total of 46 participants will be recruited from the SCUH Hepatology Clinic and will undergo a cross-sectional baseline assessment including liver FibroScans (steatosis and fibrosis), biochemical markers (liver enzymes and inflammatory cytokines, gut alpha-diversity, quality of life questionnaire, cardiovascular fitness, muscular strength, body composition and current dietary intake.
- **Study 2**: All participants will then be invited to participate in a 12-week combined (aerobic and resistance exercise) training intervention, with a mid-intervention (post week 6), and post-intervention assessment of all primary and secondary outcomes.
- **Statistical Analysis:** All outcome measures will be assessed at baseline and again at 6 and 12 weeks. Multivariate linear regression and Pearson's product-moment correlation coefficients will be used to examine relationships between the variables, and linear mixed effects modelling will assess group-time interactions (Alpha 0.05).

Discussion:

- We hypothesise that gut microbiome composition will be related to markers of chronic systemic inflammation and disease severity in MASLD patients, and that exercise training will elicit changes in gut microbiome and systemic inflammation, in line with cardiorespiratory fitness, muscular strength and body composition.
- Overall, this project aims to advance understanding of the mechanism/s through which exercise improves outcomes for MASLD patients. The findings can potentially inform the development of improved treatment options and evidence-based exercise recommendations for patients with MASLD.

AIMS

1. Identify potential relationships between gut microbiome diversity, key inflammatory markers, body composition, cardiorespiratory fitness and muscular strength in relation to the severity of MASLD.
2. Identify changes in the gut microbiome, systemic markers of inflammation, cardiorespiratory fitness, and muscular strength after a 12-week exercise intervention are related to MASLD severity.

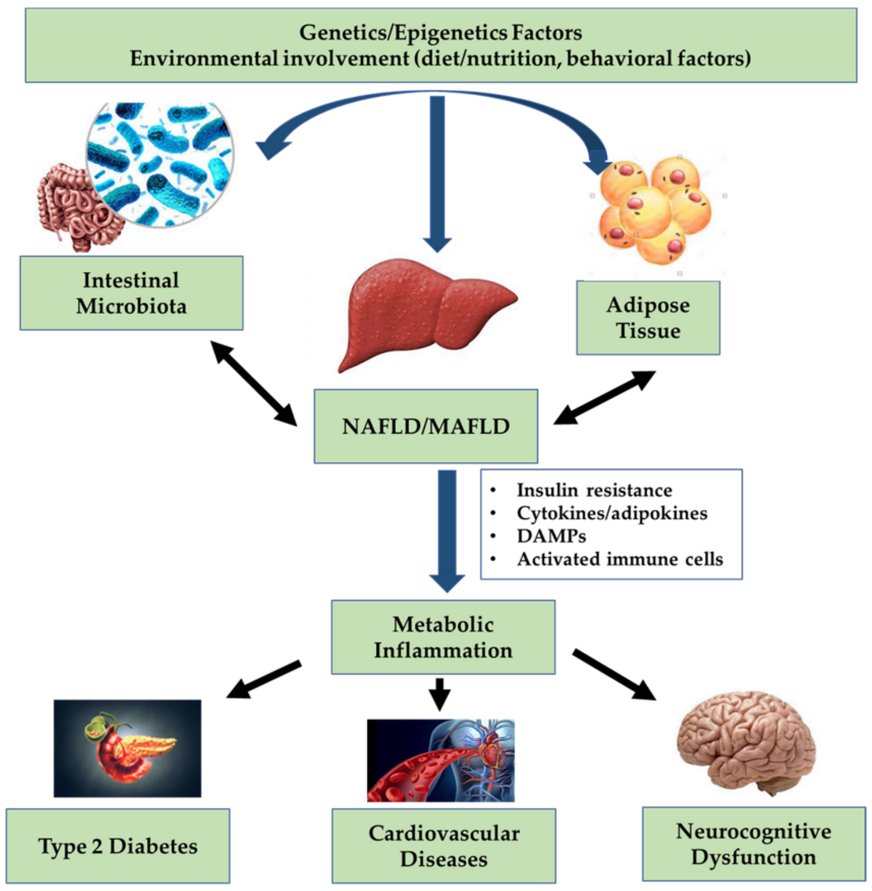
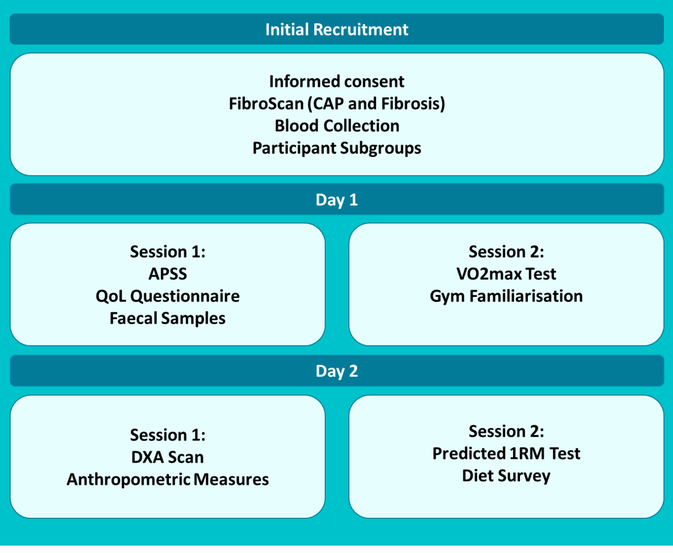


Figure 1: Factors involved in the pathogenesis of MASLDand the relationship between liver and other systemic organs involving mechanisms of disease risk and progression (3,4).

STUDY 1: CROSS-SECTIONAL



STUDY 2: LONGITUDINAL EXERCISE INTERVENTION

- 12 Weeks of Combined **Aerobic** and **Resistance** Training
- Remeasure Study 1 outcomes at **Week 6** and **Week 12**

	Aerobic Training		
Stage	Warm up	Main AT	Cool down
Duration	5 minutes	20-25 minutes	5 minutes
Intensity	30% HRR	50-60% HRR	30% HRR
RPE	10-11	12-14	10-11
	30-35 minutes		

Resistance Training		
Stage	Duration	Intensity
Warm up	1 Set	16 repetitions @ 40-50% 1RM (Major muscle groups)
Main RT	3 Sets	10-12 repetitions @ 60-70% 1RM (Can progress to 80% 1RM)

MECHANISMS

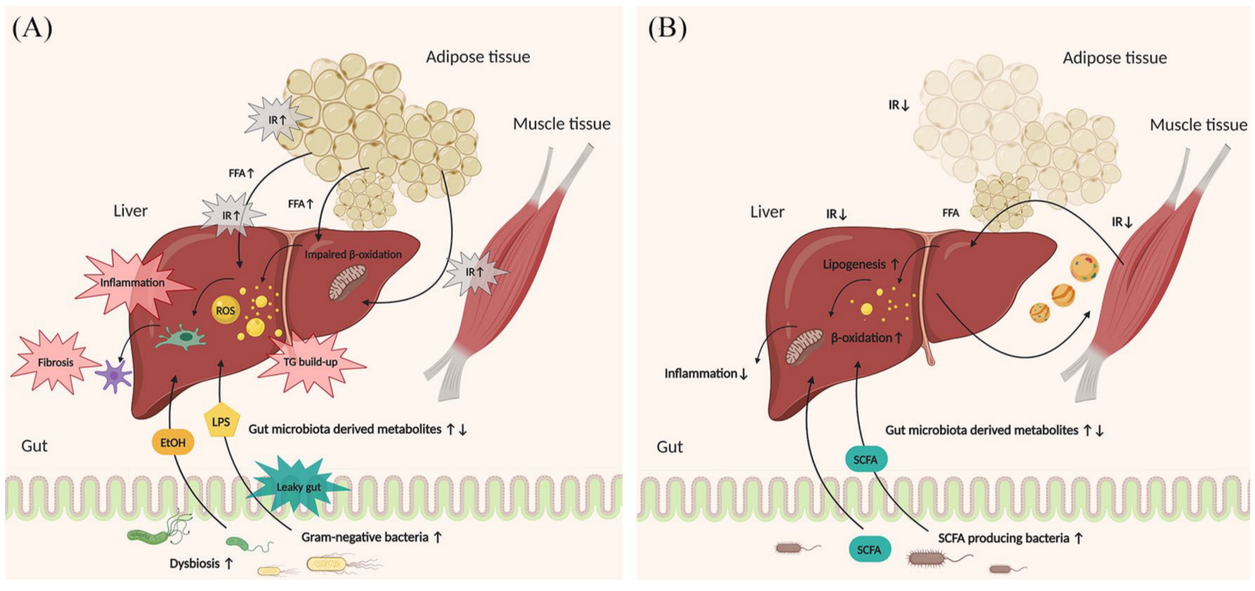


Figure 2: (A) A sedentary lifestyle and unhealthy diet lead to increased triglyceride build-up within the liver. This, along with insulin resistance in peripheral organs and the liver, triggers excessive production of reactive oxygen (ROS) species. Disproportionate ROS activates systemic inflammation and ultimately liver fibrosis. Dysbiosis and increased gut permeability allow lipopolysaccharides and ethanol compounds from gut microbiomes to reach the liver through the portal vein. This, in turn, drives lipid accumulation and inflammation in the liver. **(B)** Effects of exercise help prevent insulin resistance in the liver and peripheral organs leading to normalised lipid metabolism. Exercise improves gut microbiome composition resulting in the increase abundance of short-chain fatty acid producing bacteria. This allows more benifical metabolites to reach the liver (5).

OUTCOMES

Primary outcomes:

- Findings will advance understanding of how exercise may improve outcomes for MASLD patients through the mechanisms involved in gut microbiomes and inflammatory markers.
- Contribute to identifying the most effective type/s of exercise to improve health and outcomes for those with MASLD (potentially to prevent the progression of the disease for those at risk of its development).
- Monitor the change of gut microbiomes and inflammatory markers in relation to marks of liver disease severity/activity.

Secondary outcomes:

- Contribute to creating better diagnostic criteria regarding gut microbiomes when determining the severity of MASLD.
- Assess potential changes in quality of life of MASLD patients in response to exercise training.

References: **1**. Rinaldi, L., Pafundi, P. C., Galiero, R., Caturano, A., Morone, M. V., Silvestri, C., Giordano, M., Salvatore, T., & Sasso, F. C. (2021). Mechanisms of Non-Alcoholic Fatty Liver Disease in the Metabolic Syndrome. A Narrative Review. Antioxidants, 10(2), 270. **2**. Zhou, B.-J., Huang, G., Wang, W., Zhu, L.-H., Deng, Y.-X., He, Y.-Y., & Ma, F.-H. (2021). Intervention effects of four exercise modalities on nonalcoholic fatty liver disease: A systematic review and Bayesian network meta-analysis. European Review for Medical and Pharmacological Sciences, 25(24), 7687–7697. **3.** Rinaldi, L., Pafundi, P. C., Galiero, R., Caturano, A., Morone, M. V., Silvestri, C., Giordano, M., Salvatore, T., & Sasso, F. C. (2021). Mechanisms of Non-Alcoholic Fatty Liver Disease in the Metabolic Syndrome. A Narrative Review. Antioxidants, 10(2), 270. **4.** Niederseer, D., Wernly, B., Aigner, E., Stickel, F., & Datz, C. (2021). NAFLD and Cardiovascular Diseases: Epidemiological, Mechanistic and Therapeutic Considerations. Journal of Clinical Medicine, 10(3), 467.**5.**Houttu, V., Boulund, U., Grefhorst, A., Soeters, M. R., Pinto-Sietsma, S.-J., Nieuwdorp, M., & Holleboom, A. G. (2020). The role of the gut microbiome and exercise in non-alcoholic fatty liver disease. Therapeutic Advances in Gastroenterology, 13, 1756284820941745.

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