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Letter: proving the benefit of exercise intervention in metabolic associated fatty liver disease - authors' reply

Running Head: Letter to the Editors

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Editors:

We would like to thank Drs Stine and Schmitz[1] for their interest in our paper[2], and for their comments inviting further discussion of the interpretation of our results.

The first comment relates to the heterogeneity of the exercise group in our study, which included 16 metabolic associated fatty liver disease (MAFLD) patients across the histological spectrum. Although we acknowledge the author's comment, the decision to include patients across the entire histological spectrum of MAFLD enabled comparison to previous exercise-only studies that did not exclude non-NASH and/or cirrhotic patients and used histological endpoints[3,4]. The reporting of histological outcomes was also done to facilitate comparison with these previous studies[3,4].

As stated, this was a pilot study with the goal of informing larger randomised controlled trials on the potential benefits of aerobic exercise in improving histological features of MAFLD. Therefore, in line with the CONSORT extension for pilot and feasibility trials[5], rather than state primary outcome, as is appropriate in a definitive trial, we prespecified our assessments of a significant improvement in *any* histological endpoint of MAFLD (fibrosis and/or NAS components), similar to previous reports[3,4]. But the point of a benefit for defining outcomes in line with the FDA/EMA's intermediate endpoints is well taken.

Exercise is reported as safe and recommended for cirrhotic patients[6,7], and we argue that excluding these patients would limit our understanding of the benefits of exercise across the histological spectrum of MAFLD. Furthermore, as is common in exercise trials, our sample size was low, as acknowledged in the limitations, and we established *a priori* to analyse all included participants. It should be noted that of the 12 patients that had post-intervention liver biopsies in our study, at baseline, 11/12 (92%) had

NASH and 10/12 (83%) had fibrosis stages 1-3, while 2/12 (17%) had cirrhotic staging[2]. When restricting patients to NASH and fibrosis stages 1-3 (n=9), 5/9 (56%) achieved NASH resolution without worsening of fibrosis (*P*=0.025), 7/9 (78%) regressed one hepatocyte ballooning stage (*P*=0.008), 5/9 (56%) patients decreased NAS by ≥1-point (2-points n=2, *P*=0.023), and 5/9 (56%) regressed one fibrosis stage (*P*=0.102). We are heartened by these results which confirms the proof of concept and are not convinced that one can infer time to regression from the meta-analysis of progression data by Singh et al[8].

The authors questioned whether patients on pharmacologic treatment were included[1]. While no participants were taking any anti-NASH agents currently under investigation; as detailed in Table 1[2], at baseline some participants were taking anti-hypertensives, lipid-lowering agents and hypoglycaemic medication as part of their standard of care. We acknowledged in our limitations (Section 4.1, point e) that pharmacology was only assessed at baseline, meaning that initiation or discontinuation of medications during the intervention could not be determined.

In conclusion, we thank Drs Stine and Schmitz[1] for their comments. Our results confirm the proof of concept, and we anticipate that our data will inform the design of future randomised controlled trials to strengthen the evidence on the beneficial effects of aerobic exercise on histological endpoints of MAFLD.

Declaration of personal and financial interests

The authors' declarations of personal and financial interests are unchanged from those in the original article[2].

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