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

3 **Running Head: Letter to the Editors**

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1 **Editors:**

2 We would like to thank Drs Stine and Schmitz¹ for their interest in our paper², and for
3 their comments inviting further discussion of the interpretation of our results.

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

11 As stated, this was a pilot study with the goal of informing larger randomised controlled
12 trials on the potential benefits of aerobic exercise in improving histological features of
13 MAFLD. Therefore, in line with the CONSORT extension for pilot and feasibility trials⁵,
14 rather than state primary outcome, as is appropriate in a definitive trial, we prespecified
15 our assessments of a significant improvement in *any* histological endpoint of MAFLD
16 (fibrosis and/or NAS components), similar to previous reports^{3,4}. But the point of a
17 benefit for defining outcomes in line with the FDA/EMA's intermediate endpoints is well
18 taken.

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

1 NASH and 10/12 (83%) had fibrosis stages 1-3, while 2/12 (17%) had cirrhotic
2 staging². When restricting patients to NASH and fibrosis stages 1-3 (n=9), 5/9 (56%)
3 achieved NASH resolution without worsening of fibrosis ($P=0.025$), 7/9 (78%)
4 regressed one hepatocyte ballooning stage ($P=0.008$), 5/9 (56%) patients decreased
5 NAS by ≥ 1 -point (2-points n=2, $P=0.023$), and 5/9 (56%) regressed one fibrosis stage
6 ($P=0.102$). We are heartened by these results which confirms the proof of concept and
7 are not convinced that one can infer time to regression from the meta-analysis of
8 progression data by Singh et al⁸.

9 The authors questioned whether patients on pharmacologic treatment were included¹.
10 While no participants were taking any anti-NASH agents currently under investigation;
11 as detailed in Table 1², at baseline some participants were taking anti-hypertensives,
12 lipid-lowering agents and hypoglycaemic medication as part of their standard of care.
13 We acknowledged in our limitations (Section 4.1, point e) that pharmacology was only
14 assessed at baseline, meaning that initiation or discontinuation of medications during
15 the intervention could not be determined.

16 In conclusion, we thank Drs Stine and Schmitz¹ for their comments. Our results confirm
17 the proof of concept, and we anticipate that our data will inform the design of future
18 randomised controlled trials to strengthen the evidence on the beneficial effects of
19 aerobic exercise on histological endpoints of MAFLD.

20

21 **Declaration of personal and financial interests**

22 The authors' declarations of personal and financial interests are unchanged from those
23 in the original article².

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