NAFLD and beneficial effects of lifestyle intervention: defining the meat of the matter

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To the editor:

It is with great interest that we read the paper of Wong et al.[329] In this large population-based study, the authors address a very important issue: is lifestyle modification as important in non-obese NAFLD as it is in obese NAFLD?

Based on their study results the answer is probably yes: 67% of the non-obese patients and 61% of the obese patients had normalisation of the intrahepatic triglyceride content on MR-spectroscopy after 12 months of lifestyle intervention. The authors subsequently focus on the relative weight loss and variably advice 3–10% (abstract and lay summary) or 5–10% (discussion and conclusion) body weight loss in order to achieve this primary end point in non-obese individuals.

What is interesting, however, is that the impact of the lifestyle intervention was independent of the achieved change in absolute body weight and in waist circumference in multivariable analysis. We would therefore like to pose the question whether the authors believe it is decrease in body weight or decrease in waist circumference or maybe another component within the lifestyle intervention that reverses NAFLD? And, if the latter is true, then what could that be?

As the authors discuss themselves, body mass index (BMI) is an imperfect measure of adiposity because it cannot distinguish between fat and muscle mass.[395] Indeed, it has been found that waist-to-hip ratio is a better predictor of severe liver disease than BMI.[396] As stated above, waist circumference was indeed independently associated with reversing non-obese NAFLD in the multivariable analysis. Yet, the actual change in waist circumference over time cannot be deducted from the paper (not shown in text, tables or figures). Also, the relative weight loss (i.e. percentage of weight reduction) was in fact not analysed in multivariable fashion at all, merely the absolute change in body weight.[329]

Another matter that caught our attention (although beyond the primary outcome of this study) was the use of the fatty liver index (FLI) for the diagnosis of NAFLD after 6 years of follow-up. As known, the FLI includes waist circumference and BMI, as well as triglycerides and gamma glutamyltransferase in its algorithm.[397] The FLI was originally developed on the basis of anthropometric parameters against ultrasound and later validated against actual intrahepatic triglyceride content. However, it is exactly because of this association between anthropometrics and NAFLD, that the choice of FLI in the context of the present study is somewhat unfortunate.[329] The authors state in their results that ‘obese patients had higher FLI at year 6 compared to non-obese patients’ and that ‘obese patients were less likely to have an FLI below 30 than non-obese patients’. These findings are, although true, inherent to the algorithm and therefore redundant. As there is little data on the use of FLI as diagnostic tool for follow-up, it would have been interesting to compare the FLI at baseline against MR-spectroscopy in this study, reassuring the robustness of NAFLD diagnosis after 6 years.

In order to illustrate this point further, we validated the FLI against ultrasound (US) in our Western population-based cohort, stratified by BMI at cut-points 25kg/m² and 30kg/m². This analysis is an extension of a previous study from our group.[398] The present study consists of 5756 participants, of whom 57% is female and with a median age of 68.4 years, median BMI of 27.0 kg/m², and median FLI of 46.7.[248] We are aware of the fact that a validation of the FLI against US is suboptimal given the poor sensitivity of US for liver fat content below 25%. Nonetheless, US does have a good sensitivity for (clinically significant) moderate steatosis.[50]

As shown in *Table 1*, the FLI had a lower performance for the stratified groups than for the total group (AUROC of 0.69–0.75 in the stratified groups versus 0.80 in the total group; *Table 1*). Also, the sensitivity of FLI-defined steatosis (FLI>60) was poor in the lean (7.7%) and overweight (47.0%) population. Likewise, specificity of FLI-guided exclusion of steatosis (FLI<30) in the overweight (29.0%) and obese (2.1%) was poor as well. In addition, BMI itself can greatly affect FLI outcome. For instance, in a patient with a given set of clinical parameters (GGT: 29U/L, triglycerides: 1mmol/L, and waist circumference: 100cm) FLI could be 60.3 (including steatosis) when BMI is 30kg/m², 43.1 (inconclusive diagnosis) when BMI is 25kg/m², or 27.4 (excluding steatosis) when BMI is 20kg/m². This drives the point home that BMI affects diagnosis of steatosis when using FLI as surrogate diagnostic marker. Hence we advise against the use of the FLI as surrogate marker for steatosis in the context of examining the association between body composition and NAFLD.

That having said, we would like to emphasize our appreciation for the successful long-term follow-up after lifestyle treatment for NAFLD, a challenging target which has been rarely accomplished in the literature to date. We would therefore like to congratulate the authors with this elegant trial that addresses such an important issue.

Table 1: Validation of FLI against ultrasound-defined steatosis stratified by BMI

	All n = 5756	Lean n = 1667	Overweight n = 2727	Obese n = 1362
AUROC FLI	0.80 (0.79 – 0.81)	0.75 (0.72 – 0.79)	0.70 (0.68 – 0.72)	0.69 (0.66 – 0.72)
FLI 30				
Sensitivity	91.4	52.2	92.0	99.9
Specificity	46.9	83.1	29.0	2.1
FLI 60				
Sensitivity	62.8	7.7	47.0	92.6
Specificity	79.0	98.8	77.2	24.6

AUROC of FLI (with 95% confidence interval) was derived using the continuous measure. Stratification was carried out using the BMI cut-points 25kg/m² and 30kg/m². The total population comprises also participants with secondary causes for steatosis. Results on NAFLD instead of all-cause steatosis are similar (data not shown).
Abbreviations: AUROC – area under the receiver operator characteristic; BMI – body mass index; FLI – fatty liver index; NAFLD – non-alcoholic fatty liver disease.