in part) by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, and the Houston VA Health Services Research and Development Center of Excellence (HFP90-020). The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Acknowledgements

Letter written by Ruben Hernaez, Jennifer R. Kramer, Yan Liu and Fasiha Kanwal on behalf of all study authors.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.02.005.

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

To the Editor:

It is with great interest that we read the paper of Wong *et al.*[1] In this large population-based study, the authors address a very important issue: is lifestyle modification as important in non-obese non-alcoholic fatty liver disease (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 endpoint 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 the decrease in body weight or the 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.[2] Indeed, it has been found that waist-to-hip ratio is a better predictor of severe liver disease than BMI.[3] 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 deduced 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.[1]

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 (GGT), in its algorithm.[4] 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.[1] 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, confirming the robustness of NAFLD diagnosis after 6 years.

Received 31 December 2018; received in revised form 17 January 2019; accepted 19 January 2019

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

	All N = 5,756	Lean n = 1,667	Overweight n = 2,727	Obese n = 1,362
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

Sensititvity and specificity were calculated as percentages using descriptive statistics. AUROC of FLI (with 95% CI) was derived using the continuous measure. Stratification was carried out using the BMI cut-points 25 kg/m^2 and 30 kg/m^2. The total population comprises also participants with secondary causes for steatosis. Results on NAFLD instead of all-cause steatosis are similar (data not shown). Participants with steatosis: n = 2,057 (36%) in the total group, n = 207 (12%) in the lean group, n = 960 (35%) in the overweight group, n = 890 (65%) in the obese group. AUROC, area under the receiver operator characteristic; BMI, body mass index; FLI, fatty liver index; NAFLD, non-alcoholic fatty liver disease.

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-offs of 25 kg/m^2 and 30 kg/m^2. This analysis is an extension of a previous study from our group.[5] The present study consists of 5,756 participants, of whom 57% are female, with a median age of 68.4 years, median BMI of 27.0 kg/m^2, and median FLI of 45.7.[6] 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.[7]

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 *vs.* 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: 29 U/L, triglycerides: 1 mmol/L, and waist circumference: 100 cm) FLI could be 60.3 (including steatosis) when BMI is 30 kg/m^2, 43.1 (inconclusive diagnosis) when BMI is 25 kg/m^2, or 27.4 (excluding steatosis) when BMI is 20 kg/m^2. This drives the point home that BMI affects diagnosis of steatosis when using FLI as a 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.

Having said that, 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 on this elegant trial that addresses such an important issue.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.01.024.

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