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Establishing the independence and clinical importance of non-alcoholic fatty liver disease as a risk factor for cardiovascular disease

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To the Editor:

The evaluation of the nature of the association between non-alcoholic fatty liver disease (NAFLD) and cardiovascular risk has been the topic of a number of reports. There is emerging consensus that NAFLD is positively correlated with increased cardiovascular risk and several groups have indicated that this is independent of known risk factors.[1] The importance of this association is underlined by the observation that cardiovascular disease is a leading cause of death in individuals with NAFLD.[2, 3]

To further illuminate this topic two recent papers have been published in the Journal of Hepatology. The first of these comes from the LIDO Study Group and assesses the impact of hepatic steatosis on the incidence and development of carotid atherosclerosis.[4] Using the fatty liver index to define hepatic steatosis the authors examined associations with both carotid intima-media thickness (C-IMT) and the development of carotid plaques. In multivariable analyses hepatic steatosis was independently associated with C-IMT in a model that included a discontinuous measure of hypertension, type 2 diabetes, smoking, and age. The second paper is a systematic review and meta-analysis of studies reporting associations between NAFLD and cardiovascular events.[5] This synthesises data from 16 studies and there are several striking observations. The study designs whilst falling broadly under the term non-randomised display remarkable heterogeneity as evidenced by the high I^2 values. For instance, there are studies with both prospective and retrospective designs, studies recruiting from inpatient and outpatient settings, and endpoints that vary from in-hospital cardiovascular events only to all-cause mortality. In addition, there is little difference in the pooled odds ratio for all studies combined and the minority of those will full adjustment of confounders. This is perhaps surprising given the attenuation that one would expect with adjustment of confounding factors including age, smoking, type 2 diabetes, systolic blood pressure, and BMI.

These studies illustrate some of the challenges of determining the independence and clinical importance of the excess cardiovascular risk that may be associated with NAFLD above that of all the associated comorbid risk factors. As an example of this the use of the fatty liver index as a surrogate of hepatic steatosis raises significant questions regarding the conclusions of the study from Pais and colleagues since one of its components - waist circumference - itself is an established cardiovascular risk factor. Indeed, when the individual components of

the fatty liver index were considered in the multivariable analysis the strength of the association between C-IMT and waist circumference was similar to that of hepatic steatosis. Waist circumference acts in cardiovascular risk prediction as a surrogate of abdominal and visceral (including hepatic) adipose tissue. Whilst it is possible that hepatic steatosis is the key abnormality associated with excess cardiovascular risk[6] it is recognised that other visceral adipose tissue deposits also contribute.[7] The conclusion therefore that hepatic steatosis defined by the fatty liver index is an *independent* risk factor for carotid atherosclerosis is questionable.

The evaluation of hepatic steatosis using the fatty liver index also provides a potentially useful insight into the clinical importance of NAFLD in cardiovascular risk prediction. Assuming that waist circumference is a good surrogate of hepatic steatosis one might expect that waist circumference would provide additional, clinically important information in wider studies of cardiovascular risk. This is not the case. In a large individual patient data analysis of 58 studies, including 221,934 patients with 1.87 million person-years of follow-up, from the Emerging Risk Factors Collaboration waist circumference was associated with cardiovascular risk independently of the major known risk factors (age, gender, and smoking status).[8] That association was attenuated but persisted following further adjustment for factors including systolic blood pressure, presence of diabetes, and HDL cholesterol concentrations. Importantly however when waist circumference was added to risk prediction models it did not significantly add to the accuracy of these models. This suggests, providing information is available for systolic blood pressure, presence of diabetes, and measures of cholesterol, existing risk prediction models are likely to be applicable to patients with NAFLD and that any additional risk may be encapsulated within these. This hypothesis is supported to some extent by the higher Framingham risk scores reported for patients with NAFLD in a prior study.[9]

The hepatology community might accept that there is an increased risk of cardiovascular disease in patients with NAFLD. Further high quality prospective studies should examine the calibration of existing cardiovascular risk prediction models (for example QRISK2[10]) to determine whether these are applicable to patients with NAFLD rather than focusing on the strength and independence of the association between NAFLD and cardiovascular risk. Any miscalibration seen in such studies would serve to refine existing risk prediction models and thereby improve primary prevention strategies for patients with NAFLD.

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