Non-alcoholic fatty liver disease is associated with subclinical coronary artery disease in otherwise healthy individuals

Dear Editor,

There is a strong association between non-alcoholic fatty liver disease (NAFLD) and coronary artery disease (CAD) due to the confluence of several shared risk factors including metabolic syndrome, obesity and diabetes mellitus.^{1,2} Evidence posits that NAFLD is not merely a marker of CAD, but is independently involved in its pathogenesis, even in preclinical CAD.² Distinct ethnic differences have been noted. Comparison between Western and Eastern cohorts found that NAFLD and related metabolic complications develop within a shorter period in Asian populations, particularly in younger patients and patients with lower body mass index (BMI).³ Coronary artery calcification (CAC) is a well-established, non-invasive surrogate index that represents atherogenic risk, even within asymptomatic individuals.² Due to the potentially higher susceptibility of Asian patients to NAFLD, we studied the putative relationship between NAFLD and subclinical CAD in a healthy Asian population without known diabetes or cardiovascular disease.

The ongoing SingHEART study is a contemporary multiethnic population-based study of healthy Asian adults living in Singapore. The detailed SingHEART methodology has been published.⁴ In summary, healthy individuals aged 21–69 years old without any prior cardiovascular diseases (ischaemic heart disease, stroke and peripheral vascular disease) or diabetes were recruited from the general population from October 2015 to July 2020. Written informed consent was obtained and the study was approved by the institutional ethics review board. Data on demographics, lifestyle and medical history were collected via standardised questionnaires. Basic biochemical blood investigations including full blood counts, lipids, glucose levels and liver function tests were conducted according to standard laboratory procedures.

CAC was detected via non-contrast cardiac computed tomography (CT) scans performed on a 320x0.5mm detector row CT system. Prospective electrocardiogram triggering was used, and scans detected a single heartbeat with a gantry rotation, X-ray exposure time of 0.35 second and 0.5mm slice collimation. Coronary artery calcium scores (CACS) were calculated using the Agatston method, and classified by cut-off points of 0, 10 and 100. Hepatic steatosis was simultaneously

diagnosed by radiologists from the CT slices. NAFLD was defined as the presence of hepatic steatosis in the absence of alcohol consumption of >20g/day.

A total of 800 participants were recruited, of whom 135 (16.8%) were <30 years and did not undergo CT evaluation, and 2 refused CT evaluation. The final population comprised 663 participants. The median age was 50 years (interquartile range [IQR] 43–56), and 44.8% were men. The population had a low prevalence of diabetes (0%), obesity (5.4%), hypertension (2.4%) and hyperlipidaemia (19.0%). The overall prevalence of NAFLD was 8.3% (n=55). Participants with NAFLD versus those without were predominantly men (74.6% vs 42.1%), had a higher BMI (26.3 vs 22.8kg/m²), systolic blood pressure (142 vs 125mmHg), diastolic blood pressure (86 vs 77mmHg), triglyceride level (1.38 vs 0.96mmol/L), alanine aminotransferase level (27 vs 18U/L) and gamma-glutamyl transferase level (26 vs 22U/L). They also had a lower high-density lipoprotein cholesterol level (1.25 vs 1.41mmol/L) compared to those without hepatic steatosis. All *P* values are <0.001.

Table 1 shows the associations between NAFLD and CAC; 194 (29.3%) participants demonstrated coronary artery calcification (CACS>0), 147 (22.2%) had CACS>10, and 60 (9.04%) had CACS>100. Participants with NAFLD vs those without were more likely to have CACS>0 (43.6% vs 28.0%, *P*=0.014) and CACS>10 (38.2% vs 20.7%, *P*=0.003). Logistic regression models with odds ratios (OR) and 95% confidence intervals (CI) were further used to assess the independent associations between NAFLD and CAC. In univariate models, the presence of NAFLD was significantly associated with CACS>0 (OR 1.99, 95% CI 1.14–3.50, *P*=0.016) and CACS>10 (OR 2.35, 95% CI 1.31–4.24, *P*=0.004) but not CACS>100 (*P*=0.159). After multivariable adjustment for confounders, the association between NAFLD and CACS>0 was attenuated (*P*=0.119). However, NAFLD was still significantly associated with a CACS>10 (OR 2.19, 95% CI 1.01–4.76). The sensitivity and specificity for NAFLD for the presence of CACS>0 and CACS>10 were 12.4%, 93.4% and 14.3%, 93.4%, respectively. In subgroup analysis, there were no significant interactions between NAFLD and CACS by sex or obesity (*P*_{interaction}>0.05).

Table 1. Association between non-alcoholic fatty liver disease (NAFLD) and varying severities of coronary artery calcification (CAC)

Outcome ^d	Overall (n=663)	NAFLD (n=55)	No NAFLD (n=608)	Model 1 ^a		Model 2 ^b		Model 3 ^c	
				P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)
CACS>0	194 (29.3)	24 (43.6)	170 (28.0)	0.014	1.99 (1.14–3.50)	0.016	1.89 (0.98–3.65)	0.058	1.76 (0.86–3.59)
CACS>10 ^d	147 (22.2)	21 (38.2)	126 (20.7)	0.003	2.35 (1.31–4.24)	0.004	2.29 (1.13–4.65)	0.022	2.19 (1.01–4.76)
CACS>100 ^d	60 (9.05)	7 (12.7)	53 (8.72)	0.321	1.87 (0.78–4.45)	0.159	1.45 (0.47–4.48)	0.515	1.26 (0.37–4.30)

CI: confidence interval

^a No adjustment for confounders^b Adjusted for age and sex^c Multivariable adjustment for age, sex, smoking, sedentary lifestyle, systolic blood pressure, body mass index, low-density lipoprotein cholesterol, triglyceride and glucose^d Outcomes calculated in reference to participants with no CAC (CACS=0)

Significant values are in bold.

This study highlights the following significant findings in a healthy Asian population: participants with NAFLD had significantly higher burden of metabolic risk factors, and there was an independent association between NAFLD and at least mild coronary artery calcification (CACS>10).

The prevalence of NAFLD was 8.3% in our healthy cohort, lower than the reported prevalence rates within general Asian communities that range from 9–45%, according to a review by Farrell et al. in 2013.⁵ This disparity could be due to the healthier composition of our cohort compared to the other studies conducted on general populations (patients with diabetes and cardiovascular diseases were excluded in our cohort). Nonetheless, even among these healthy participants, NAFLD was associated with a higher burden of metabolic risk factors including higher blood pressure, BMI, glucose and lipid levels, similar to previously reported studies.⁶

A positive calcium score reflects the presence of atherosclerotic plaque burden, and is considered a sensitive and specific predictor in identifying CAD.⁷ There is strong evidence of association between CAC and NAFLD across various cohorts^{8,9} and our study lends further support to this in a “low risk” Asian population. Our cohort of Asian participants were healthy, free of prior cardiovascular diseases, and had a favourable metabolic profile with a low prevalence of diabetes, obesity and hypertension. Nonetheless, our study still demonstrates a significant association between NAFLD and at least mild CAC within these individuals. These findings—including the high specificity of NAFLD for the presence of CAC—have important clinical implications, and suggest that the presence of NAFLD even within this relatively healthy cohort should prompt optimal preventive strategies to minimise future cardiovascular risk. While no significant association was found between CACS>100 in this study, this could be potentially attributed to the low prevalence of CACS>100 (60/633, 9.5%) in this relatively healthy cohort.

Limitations of our study include the relatively small sample size, the use of only CT for diagnosis of NAFLD (reported by experienced radiologists, albeit without fixed criteria) and the cross-sectional nature of this study with absence of longer-term hard outcomes. In addition, data on the severity of NAFLD was not available. These findings should be validated in larger cohorts.

In conclusion, NAFLD is not uncommon even in a healthy population that suggests lower risk, and is shown to be associated with at least mild subclinical

coronary atherosclerosis. This highlights a subset population who may benefit from preventive strategies to mitigate progression to known cardiovascular diseases.

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