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Non-alcoholic fatty liver modifies associations of body mass index and waist circumference with cardiometabolic risk: The CARDIA study

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is recognized as a prevalent determinant of cardiometabolic diseases. The association between NAFLD and obesity warrants further research on how NAFLD modifies associations between body mass index (BMI) and Waist circumference (WC) with cardiometabolic risk (CMR).

Objective: This study assessed whether NAFLD modifies associations between BMI and WC with 5-year changes in CMR in 2366 CARDIA study participants.

Methods: Non-contrast CT was used to quantify liver attenuation, with ≤51 Hounsfield Units (HU) used to define NAFLD in the absence of secondary causes of excess liver fat. The dependent variable was the average Z score of fasting glucose, insulin, triglycerides [log], (–) high-density lipoprotein cholesterol (HDL-C), and systolic blood pressure(SBP). Multivariable linear regression was used to estimate the associations between BMI and WC with CMR. Effect modification by NAFLD was assessed by an interaction term between NAFLD and BMI or WC.

Results: The final sample had 539 (23%) NAFLD cases. NAFLD modified the association of BMI and WC with CMR (interaction $p < 0.0001$ for both). BMI and WC were associated with CMR in participants *without* NAFLD ($p < 0.001$), but not among those *with* NAFLD. Participants *with* NAFLD and *normal* BMI and WC had CMR estimates that were higher than those *without* NAFLD in the *obese* categories. Among those *without* NAFLD the 5 years CMR change estimate was 0.09 (95% CI: 0.062, 0.125) for BMI ≥30 kg/m^2 compared to −0.06 (−0.092, −0.018) for BMI < 25 kg/m^2, and among those *with* NAFLD, these estimates were 0.15 (0.108, 0.193) and 0.16 (−0.035, 0.363).

Conclusions: NAFLD modifies associations of BMI and WC with CMR. Compared with BMI and WC, NAFLD was more strongly associated with CMR. In the presence of NAFLD, BMI and WC were not associated with CMR. These findings have implications for clinical screening guidelines.

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KEYWORDS
cardiovascular disease, cohort, epidemiology, liver disease, obesity

1 | INTRODUCTION

NAFLD is characterized by potentially harmful levels of fat accumulation in the liver. NAFLD is diagnosed when ≥5% of the liver parenchyma contains fat, determined by liver imaging techniques or biopsy in the absence of any secondary causes of hepatic fat accumulation. NAFLD is the leading cause of chronic liver disease in the U.S,[1] and is an increasingly recognized contributor to cardiometabolic diseases.[2,3] Indeed, patients with NAFLD are at higher risk of diabetes, metabolic syndrome, and cardiovascular disease relative to those without NAFLD.[4–8]

NAFLD is asymptomatic and typically goes undetected, and thus untreated, until the later stage manifestations of non-alcoholic steatohepatitis (NASH). Although the exact figures are unknown, it is estimated that 21%–25% of the general global population, and up to 80%–90% of individuals with obesity, have NAFLD.[9–11] Higher BMI has been associated with higher incidence and prevalence of NAFLD.[12,13] However, measures of WC and visceral fat distribution, as assessed via ultrasound, computed tomography, or magnetic resonance imaging, have been found to be more strongly associated with NAFLD when compared to BMI.[14–16] These studies have contributed to a growing body of literature reporting central obesity to be associated with adverse health outcomes and mortality, independent of BMI,[17] likely resulting from the more metabolically active nature of visceral adipose tissue (VAT) versus fat depots in other areas of the body (e.g., gluteal-femoral).[18,19] Although several studies have assessed the associations between NAFLD and cardiometabolic outcomes,[20–23] the extent to which NAFLD status, because of its causal impact on cardiometabolic pathways, may modify the associations between traditional anthropometric measurements (i.e., BMI and WC) and cardiometabolic outcomes has not been studied in detail.

The purpose of this 5-year longitudinal study was to examine the extent to which NAFLD modifies the association between BMI or WC and changes in CMR, comprising SBP, HDL-C cholesterol, and fasting insulin, glucose, and triglycerides in a prospective bi-racial cohort of adult men and women over a period of 5 years. The hypothesis for the study was - relative to adults without NAFLD, those with NAFLD would have larger increases in CMR independent of BMI and WC, and that the associations between BMI and WC with CMR risk would be modified by NAFLD status.

2 | METHODS

Briefly, the Coronary Artery Risk Development in Young Adults (CARDIA) study is a prospective, multi-center cohort started in 1985–86, designed to investigate the development and correlates of cardiovascular disease and its associated risk factors in young adults. A total of 5115 black and white men and women (between 18 and 30 years) from 4 US cities (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California) participated in the baseline examination. The baseline examination (Year 0; 1985/86), employed standardized measures for known cardiovascular risk factors, including biological, psychosocial, demographic, and lifestyle factors. Follow-up visits and re-examinations were completed 2, 5, 7, 10, 15, 20, 25, and 30 years after the baseline examination. The participant retention for each follow-up visit was 91%, 86%, 81%, 79%, 74%, 72%, 72%, and 71% of the surviving cohort. Institutional Review Board approvals were obtained for each field center and informed consent was obtained from all participants prior to enrollment.

2.1 | Inclusion and exclusion criteria

The target population for the study was participants in whom the variables of interest were assessed at both Year 25 (2010/11) and Year 30 (2015/16) of the CARDIA study. CARDIA participants with complete Y25 measurements of liver fat (CT-derived liver attenuation performed at Y25 only), BMI, WC, and cardiometabolic indices were potentially eligible in this study (n = 2712). Based on self-reported questionnaires, participants with prevalent liver disease and secondary causes of liver fat such as hepatitis/cirrhosis (n = 52), heavy alcohol consumption (>14 drinks/week for women and >21 drinks/week for men; n = 208), or self-reported HIV or prior IV drug use (n = 26), use of medications with risk of hepatic steatosis (valproic acid, methotrexate, tamoxifen, or amiodarone; n = 45), and those with missing values for any of the predictor variables were excluded (from self-reported questionnaires), leaving a final analytical sample size of 2366.

2.2 | Measures

The participants were asked to fast overnight for 12 h before each clinical examination and were asked to avoid using tobacco, engaging in strenuous physical activity, or consuming caffeine or alcohol. BP was measured using a standard automated BP measurement monitor (Omron model HEM907XL) and was calculated as an average of the 2nd and 3rd SBP readings. Blood samples were collected via routine phlebotomy, processed and frozen for later laboratory assays for blood lipids, glucose, and insulin. Height of each participant was measured in centimeters using an anthropometric ruler or stadiometer. Weight was measured using a Detecto Scale (Model #68965 or #68967). BMI was calculated as kg/m^2. WC was measured using a

Gulick II Plus anthropometric tape in centimeters (Model #67019) midway between the iliac crest and the bottom of the rib cage. An average of two WC measures at Year 25 was used as the measure of WC. BMI was categorized as normal weight (<25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2). Cut-offs of 102 cm for men and 88 cm for women were used to categorize WC into central obesity versus non-obese.[24,25]

Alcohol intake was assessed at each examination with the following question, "Did you drink any alcoholic beverages in the past week?" and, with the use of visual aids to demonstrate a typical drink, we asked three follow-up questions to assess the number of drinks of wine, beer, and liquor typically consumed in a week. Total ethanol consumption in milliliters of ethanol per day was calculated as per the CARDIA protocol (assuming 1 drink of beer, wine, or liquor contains 16.7 mL, 17.0 mL, or 19.2 mL of ethanol, respectively).[26,27] Smoking status was assessed as never, former, and current, while education status was assessed as at more than high school or high school or less. More details of the standardized protocols for all the examinations (including BP measurements, anthropometrics, phlebotomy, imaging techniques, and structured questionnaires on socio-demographics, medical and family history, psychosocial characteristics, and diet, among others) are described elsewhere.[28–30]

2.3 | Assessment of NAFLD

In CARDIA, liver attenuation in Hounsfield Units (HU) was measured on 2.5 mm thick non-contrast CT images acquired using multi-detector 64-slice GE 750HD and LightSpeed VCT (GE Healthcare, Waukesha, Wisconsin) at the Birmingham and Oakland Centers, respectively, and Siemens Sensation 64-slice (Siemens Medical Solutions) at the Chicago and Minneapolis Centers. The multi-center computed tomography (CT) protocol used in CARDIA and liver attenuation measurements have been described in detail.[2,31–33] Image analysis was performed at a core reading center (Wake Forest University Health Sciences). Liver attenuation was measured in the right lobe of the liver on axial CT slices through the upper abdomen using the NIH Center of Information Technology Medical Image Processing, Analysis, and Visualization (MIPAV) application. Liver attenuation is the average of nine measurements in three 2.6 cm^2 circular regions of interest on each of the three CT slices. Trained readers placed liver regions of interest avoiding the large vessels and lesions. The interclass correlation coefficient for liver attenuation was 0.975 in blinded re-reading of a random sample of 156 participants. This study used a non-contrast CT measured liver attenuation cut-off of ≤40 Hounsfield Units (HU) (approximates moderate-to-severe steatosis)[34] and ≤51 HU (equivalent to liver: spleen ratio <1; at least mild steatosis) to diagnose NAFLD when no other potential secondary cause(s) of liver fat accumulation was present. NAFLD was defined as ≤51 HU to increase statistical power and reduce misclassification, while results based on ≤40 HU are provided in supplementary tables.

2.4 | Cardiometabolic risk score (CMR)

The dependent variable was a clustered CMR based on the CARDIA Y25 means and SDs of the following risk factors: fasting glucose, insulin, triglycerides [natural log], HDL-C, and SBP.[35,36] Z-scores were computed for each risk factor for each CARDIA participant at Y25 and Y30, and each participant's CMR was computed as the mean of the Z-scores. In computing the mean, HDL-C was subtracted rather than added due to its inverse association with other CMR factors. Five-year change in CMR, the dependent variable of this longitudinal study, was computed as the Y25 value subtracted from the Y30 value.

2.5 | Statistical analysis

SAS 9.4 was used for all statistical analyses. The analysis used multivariable linear regression with 5-year CMR change (CARDIA Y25 to Y30) as the normally distributed dependent variable. The independent variables of interest were NAFLD, BMI, WC, and the interaction terms of NAFLD and continuous BMI, and NAFLD and continuous WC. Collinearity was not a concern because the correlations between BMI or WC and liver attenuation were low to moderate among those with (~0.1 to 0.3) and without (~0.2 to 0.4) NAFLD. Covariates in the models were Year 25 CMR, age, sex, race, education, cigarette smoking, alcohol intake, and use of diabetes, hypertension, and hyperlipidemia medications. To interpret the interactions between NAFLD and BMI, and NAFLD and WC, the models were repeated with categorical BMI (normal weight, overweight, and obese) and WC (non-obese and obese) to estimate the adjusted least squares means for each of the six BMI × NAFLD and four WC × NAFLD categories.

3 | RESULTS

Out of the total sample of 2366, 539 (23%) were classified as positive for NAFLD based on the ≤51 HU threshold. Table 1 presents Year 25 demographics and other baseline characteristics stratified by NAFLD status. The average age of the sample at Year 25 (2010/11) was 50.1 (SD = 3.6) years with 42.6% males and 57.4% females. There were 311 cases (57.7%) of NAFLD in males and 228 cases (42.3%) in females. At year 25, participants with NAFLD had markedly higher mean values of fasting glucose, insulin, triglycerides, SBP, and WC compared with those without NAFLD, whereas mean HDL-C was 48.4 mg/dl in participants with NAFLD and 60.1 mg/dl in participants without NAFLD. Normal weight, overweight, and obese, respectively, formed 2.8%, 20.4% and 76.8% of those with NAFLD, and 29.6%, 35.3% and 35.1% of those without NAFLD, respectively.

In fully adjusted models with 5-year change in CMR as the dependent variable, we observed strong interactions between continuous BMI and NAFLD ($p \leq 0.0001$), as well as continuous WC and NAFLD ($p \leq 0.0001$). The associations between BMI and WC

TABLE 1 Year 25 characteristics of the CARDIA study sample by NAFLD status (≤51 HU).

	Total (n = 2366)	No NAFLD (n = 1827)	NAFLD (n = 539)
Age (years)	50.1 (3.6)	50.0 (3.6)	50.3 (3.6)
Sex (n, %)			
Male	1008 (42.6)	697 (38.2)	311 (57.7)
Female	1358 (57.4)	1130 (61.8)	228 (42.3)
Race			
Black	1117 (47.2)	877 (48.0)	240 (44.5)
White	1249 (52.8)	950 (52.0)	299 (55.5)
Education			
High school or less	501 (21.1%)	389 (21.3%)	112 (20.8%)
More than high school	1865 (78.9%)	1438 (78.7%)	427 (79.2%)
Alcohol intake (ml/day)	7.4 (10.7)	7.3 (10.4)	7.9 (11.8)
Smoking			
Never	1531 (64.7%)	1204 (65.9%)	327 (60.7%)
Former	509 (21.5%)	369 (20.2%)	140 (26.0%)
Current	326 (13.8%)	254 (13.9%)	72 (13.3%)
Fasting glucose (mg/dl)	99.0 (27.4)	94.9 (20.7)	112.8 (40.1)
Fasting insulin (IU/mL)	11.4 (10.1)	9.4 (8.7)	18.2 (11.3)
HDL-C (mg/dl)	57.5 (17.2)	60.1 (17.4)	48.4 (13.2)
LDL cholesterol (mg/dl)	112.4 (32.3)	112.6 (32.1)	111.7 (33.0)
Fasting triglycerides (mg/dl)	112.5 (79.6)	99.7 (61.0)	156.0 (112.9)
SBP (mmHg)	119 (15.8)	118 (15.6)	124 (15.5)
WC			
Normal	1281 (54.1%)	1169 (64.0%)	112 (20.8%)
Obese (≥88 cm women, ≥100 cm men)	1085 (45.9%)	658 (36.0%)	427 (79.2%)
BMI			
<25 kg/m^2	556 (23.5%)	541 (29.6%)	15 (2.8%)
25–29.9 kg/m^2	754 (31.9%)	644 (35.3%)	110 (20.4%)
≥30 kg/m^2	1056 (44.6%)	642 (35.1%)	414 (76.8%)
Taking medications for diabetes/hypertension/lipids			
No medication	1555 (65.7%)	1284 (70.3%)	271 (50.3%)
1 medication	502 (21.2%)	361 (19.8%)	141 (26.2%)
>1 medication	309 (13.1%)	182 (10.0%)	127 (23.6%)
Liver attenuation (HU)	55.7 (11.8)	60.7 (5.9)	38.9 (11.4)

Note: Data are mean (sd) or n (%).

and 5-year CMR change are shown in Table 2, stratified by NAFLD status. BMI and WC were strongly and independently associated with CMR changes among participants *without* NAFLD, but not among those *with* NAFLD. For example, among those *without* NAFLD, the CMR change estimate was 0.09 (95% CI: 0.062, 0.125) for BMI ≥30 kg/m^2 compared to −0.06 (−0.092, −0.018) for BMI <25 kg/m^2, and among those *with* NAFLD, these estimates were 0.15 (0.108, 0.193) and 0.16 (−0.035, 0.363). The differences were larger between the two WC categories for those without NAFLD. However, among participants *with* NAFLD, BMI and WC had no association with CMR changes. The results of analyses with NAFLD defined as ≤40 Hounsfield Units are shown in Supplementary Table S1, with similar results, although statistical power was lower (yielding wider confidence intervals).

TABLE 2 Mean 5-year changes in CMR (95% CIs) according to BMI and WC categories, stratified by Y25 NAFLD (≤51 HU).

	No NAFLD (n = 1827)	NAFLD (n = 539)
BMI (kg/m^2)		
<25 (n = 556)	−0.055 (−0.092, −0.018)	0.164 (−0.035, 0.363)
25–29.9 (n = 754)	0.050 (0.019, 0.080)	0.117 (0.042, 0.191)
≥30 (n = 1056)	0.094 (0.062, 0.125)	0.151 (0.108, 0.193)
WC (cm)		
<88 W, <100 M (n = 1281)	−0.011 (−0.035, 0.014)	0.104 (0.030, 0.178)
≥88 W, ≥100 M (n = 1085)	0.117 (0.085, 0.148)	0.150 (0.108, 0.192)

Note: Separate models for BMI and WC. Each model included the main effect for BMI or WC, the main effect for NAFLD, the interaction term for NAFLD × BMI or NAFLD × WC, Year 25 CMR, and all covariates. Data are adjusted least squares means and 95% confidence intervals estimated from the multivariable linear regression models. The covariates included baseline CMR, age, sex, race, education, smoking status, alcohol (ml/day), medications for diabetes, hypertension, and hyperlipidemia.

Abbreviations: CMR, cardiometabolic risk score; M, men; W, women.

Figures 1 and 2 present the Year 30 CMR means adjusted for Year 25 CMR, as well as the other covariates, stratified by BMI category and NAFLD (Figure 1) and by WC category and NAFLD (Figure 2). NAFLD status was significantly associated with CMR across all BMI and WC categories. Participants *with* NAFLD in the lowest BMI and WC categories had mean CMR estimates higher than participants *without* NAFLD in the highest BMI and WC categories.

4 | DISCUSSION

The results suggest that NAFLD status considerably modified the association of both BMI and WC with the 5-year change in CMR in middle-aged men and women in the CARDIA Study. As expected, BMI and WC were strongly associated with cardiometabolic risk in participants without NAFLD. However, among those with NAFLD, BMI and WC had no association with CMR change. This study appears to be the first epidemiologic cohort study to assess the interaction between NAFLD and routine clinical measures of general and central obesity in the US population. The magnitude and nature of this interaction was quite strong and striking, especially given the subclinical nature and high prevalence of NAFLD in the population.

The effect modifying nature of NAFLD on the association of BMI and WC with CMR has potentially important clinical and epidemiological implications. A lack of association between BMI and WC with CMR in the presence of NAFLD suggests a fundamental etiologic role of NAFLD, independent of the traditional anthropometric measures widely used in clinical practice. This finding is notable in the context of the high prevalence of NAFLD in middle age and the lack of recommendations for NAFLD screening in clinical practice. Though NAFLD prevalence is lower in lean than in overweight individuals,[37] studies have found a higher incidence of metabolic outcomes in individuals with lean NAFLD compared with those without NAFLD.[37–41] Interestingly, a 7-year prospective cohort study from Sri Lanka found similar risks of developing incident metabolic comorbidities between lean and non-lean cases of NAFLD.[42] The results of the current study show that NAFLD was more strongly associated with CMR than anthropometric indicators of obesity, and therefore, in the presence of NAFLD, anthropometric indicators of obesity (BMI and WC) were not associated with CMR. These findings suggest that using BMI and WC alone to assess CMR may need to be reconsidered. Indeed, our findings are informative for potential recommendations for routine NAFLD screening. Still, it is important to recognize the importance and clinical significance of BMI and WC, and our findings acknowledge the well understood association of these traditional anthropometric measures with CMR.

Our findings lend support to the accumulating literature of a "lean metabolically unfit" phenotype that may have a high prevalence within and across populations.[37–40] Indeed, some populations may be more predisposed to NAFLD outside of general obesity, such as South and Southeast Asian populations.[41] Although the exact etiology and pathophysiology of NAFLD in lean patients is unclear, various pathways have been proposed, including "dysfunctional fat", genetic background (e.g., PNPLA3 polymorphisms), and epigenetic changes early in life.[43] Lifestyle factors including diet, physical activity, and smoking are strong environmental influencers of CMR, and may have important associations with intra-abdominal fat depots independent of BMI or WC.[44,45] Regardless of the upstream causes of excess hepatic fat accumulation in lean and obese individuals, NAFLD has emerged as a robust, causal determinant of cardiometabolic risk[2,6–8] Valid and feasible clinical tools, such as quantitative ultrasound, for NAFLD screening further enhance the potential implications of our findings.[46,47]

Limitations of the current study include the use of CT to measure liver fat, which has a lower sensitivity than MRI. This study uses noncontrast CT to measure NAFLD, while in real world setting, liver fat is often an unpremeditated finding in routine USG. Though non-noncontrast CT is a more sensitive measure of liver fat compared to USG,[46] use of CT for routine detection of NAFLD may not be a feasible option in some clinical settings. This may affect the generalizability of

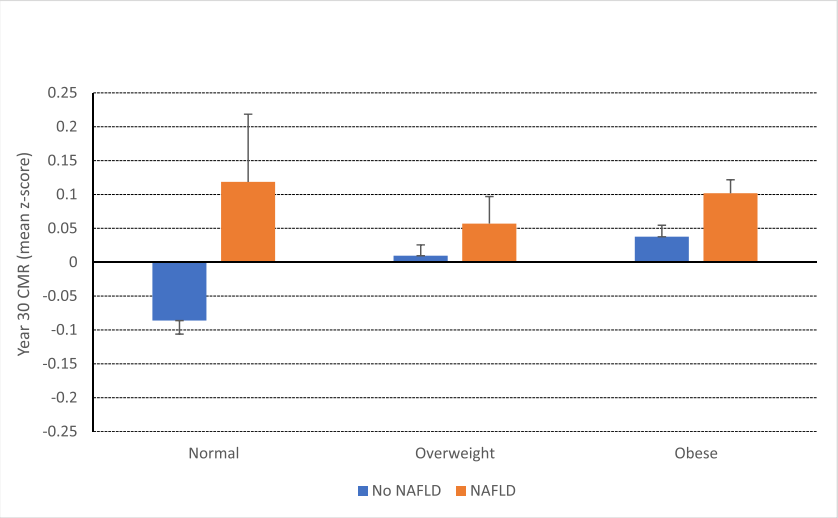

FIGURE 1 Year 30 CMR (mean z-score) adjusted for Year 25 CMR and covariates, stratified by BMI category and NAFLD status.

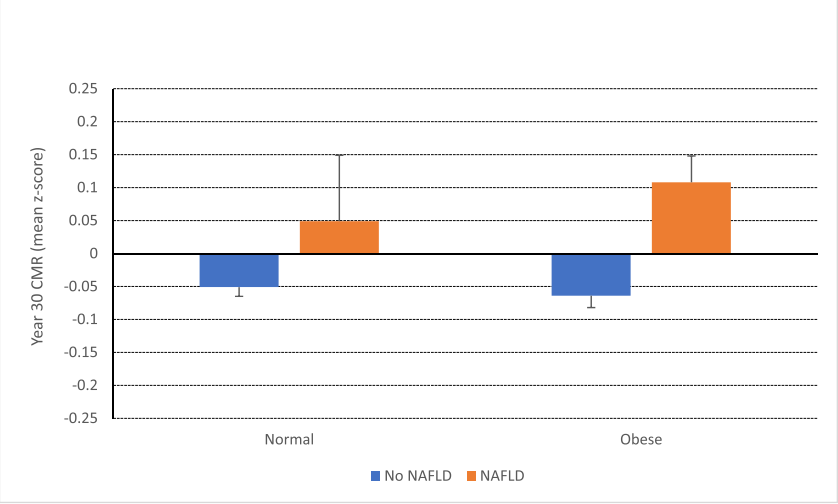

FIGURE 2 Year 30 CMR (mean z-score) adjusted for Year 25 CMR and covariates, stratified by WC category and NAFLD status.

the results to the general population, but these results based on a more sensitive and accurate measure of NAFLD will help the clinicians to better understand the cardiometabolic risks of subclinical NAFLD, and take proactive measures to identify those with this slowly progressive but perilous condition. This study did not examine differences by race, sex, or diabetes status/medication because of low statistical power for further stratifications. Additionally, this study did not assess liver disease severity (e.g., fibrosis measures), or duration of NAFLD because of lack of these measures. However, the consistency in the results comparing the two NAFLD definitions supports internal validity. The use of BMI as one of the anthropometric measures for the analysis may be a potential limitation in the view of some recent studies suggesting BMI to be an inaccurate proxy for cardiometabolic risk.[48] This concern was addressed by using WC as a second anthropometric measure in the study. The results suggested a similar and consistent trend in the BMI and WC categories. Strengths include the multi-center community-based population, the large sample size, the objective clinical measures of anthropometry and cardiometabolic risk factors, well characterized covariates, and the longitudinal design of the CARDIA Study.

To conclude, the study findings suggest that NAFLD is more strongly associated with CMR than anthropometric indicators of obesity, and therefore, in the presence of NAFLD, anthropometric indicators of obesity (BMI and WC) were not associated with CMR. These results provide further support for the insidious role of subclinical NAFLD in the etiology of cardiometabolic risk. The findings shed light on an intriguing, strong interaction between NAFLD and general obesity assessed by BMI and WC, which may have implications for routine clinical screening guidelines, risk prediction, and stratification.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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