Association of Nonalcoholic Fatty Liver Disease With Subclinical Myocardial Remodeling and Dysfunction: A Population-Based Study

Lisa B. VanWagner,¹,² Jane E. Wilcox,¹,³ Laura A. Colangelo,¹ Donald M. Lloyd-Jones,¹,³ J. Jeffrey Carr,⁴ João A. Lima,⁵ Cora E. Lewis,⁶ Mary E. Rinella,² and Sanjiv J. Shah³

Nonalcoholic fatty liver disease (NAFLD) and heart failure (HF) are obesity-related conditions with high cardiovascular mortality. Whether NAFLD is independently associated with subclinical myocardial remodeling or dysfunction among the general population is unknown. We performed a cross-sectional analysis of 2,713 participants from the multicenter, community-based Coronary Artery Risk Development in Young Adults (CARDIA) study who underwent concurrent computed tomography (CT) quantification of liver fat and comprehensive echocardiography with myocardial strain measured by speckle tracking during the Year-25 examination (age, 43-55 years; 58.8% female and 48.0% black). NAFLD was defined as liver attenuation ≤40 Hounsfield units after excluding other causes of liver fat. Subclinical left ventricular (LV) systolic dysfunction was defined using values of absolute peak global longitudinal strain (GLS). Diastolic dysfunction was defined using Doppler and tissue Doppler imaging markers. Prevalence of NAFLD was 10.0%. Participants with NAFLD had lower early diastolic relaxation (e') velocity (10.8 ± 2.6 vs. 11.9 ± 2.8 cm/s), higher LV filling pressure (E/e' ratio: 7.7 ± 2.6 vs. 7.0 ± 2.3), and worse absolute GLS (14.2 ± 2.4% vs. 15.2 ± 2.4%) than non-NAFLD (P < 0.0001 for all). When adjusted for HF risk factors or body mass index, NAFLD remained associated with subclinical myocardial remodeling and dysfunction (P < 0.01). The association of NAFLD with e' velocity (β = -0.36 [standard error = 0.15] cm/s; P = 0.02), E/e' ratio (β = 0.35 [0.16]; P = 0.03), and GLS (β = -0.42 [0.18]%; P = 0.02) was attenuated after controlling for visceral adipose tissue. Effect modification by race and sex was not observed. Conclusions: NAFLD is independently associated with subclinical myocardial remodeling and dysfunction and provides further insight into a possible link between NAFLD and HF. (HEPATOLOGY 2015; 00:000-000)

Both heart failure (HF) and nonalcoholic fatty liver disease (NAFLD) are obesity-related conditions with high cardiovascular morbidity and mortality that have reached epidemic proportions.¹-³ Growing evidence suggests that NAFLD is an independent risk factor for cardiovascular disease (CVD) and is associated with impaired endothelial function,⁴ a higher prevalence of vulnerable coronary plaques,⁵,⁶ and with unfavorable levels of markers of subclinical atherosclerotic disease, including increased carotid intima media thickness⁷ and coronary artery calcification (CAC).⁸-¹⁰ In fact, patients with NAFLD are more likely to die...
from complications of CVD than from liver-related death. Small studies of selected patients, primarily in adolescents, have found that NAFLD is also associated with myocardial insulin resistance (IR), altered cardiac energy metabolism, abnormal left ventricular (LV) structure, and impaired diastolic function. However, whether these associations between NAFLD and abnormalities in myocardial structure and function apply to the general adult population is unknown.

Visceral adipose tissue (VAT) is an endocrine organ that secretes factors contributing to vascular inflammation and IR and may be a risk factor for NAFLD or a marker of NAFLD severity. Given that NAFLD and metabolic syndrome (MetS) features often coexist, any relationship between NAFLD and cardiac remodeling and dysfunction may be moderated by VAT volume, obesity, or other cardiometabolic risk factors. To date, it remains unclear whether the associations between NAFLD and subclinical abnormalities in myocardial structure and function are independent of these factors. Improved knowledge of the mechanisms underlying any observed associations may provide pathophysiological insight into a possible link between NAFLD and clinical HF.

Therefore, we sought to examine the associations between NAFLD and early changes in LV structure and function in a population-based study and whether the strengths of these associations were influenced by cardiometabolic risk factors, including other markers of adiposity. We hypothesized that NAFLD is significantly associated with subclinical abnormalities in cardiac structure and function, even after adjustment for body mass index (BMI) and VAT.

Patients and Methods

Study Sample. CARDIA is a multicenter, community-based, longitudinal cohort study of the development and determinants of CVD in black and white young adults recruited from 1985 to 1986 at 18-30 years of age across four U.S. cities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). The study design has been published previously. Eight examinations have been completed to date, which were approved by institutional review boards at all sites and informed consent obtained at every examination. The present study includes participants who underwent both comprehensive echocardiography (including tissue Doppler imaging and speckle-tracking analysis) and computed tomography (CT) scanning of both the thorax and abdomen from June 2010 to August 2011 as part of the 25-year follow-up examination.

There were 3,498 participants (45.5% male, 50.5% black) that attended the CARDIA Year-25 exam. Participants were excluded from the CT exam if they were pregnant, weighed more than 450 lbs, or were unable to fit within the CT gantry (n = 28). We also excluded those missing measurements for liver fat (n = 304), those without an echocardiogram or with poor speckle-tracked images (n = 27), 62 participants with a medically verified history of acute myocardial infarction (MI), angina or HF, those with a self-reported history of hepatitis C or cirrhosis (n = 30), and those with a risk factor for chronic liver disease (CLD; e.g., intravenous drug use [IDU]) or with a potential cause of secondary hepatic steatosis (HS; n = 338): alcohol consumption ≥20 g/day in women and ≥30 g/day in men (n = 179), self-reported human immunodeficiency virus (HIV; n = 22), previous IDU (n = 93), and medications known to cause HS (e.g., valproic acid, methotrexate, tamoxifen, and/or amiodarone; n = 44). The remaining 2,713 participants formed the sample population (Fig. 1).

Measurements. Standardized protocols for data collection were used across study centers, and measurements have previously been described. CT. The CT protocol included the heart and abdomen using a noncontrast CT scan performed using GE
was performed using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Otawara, Japan) by trained sonographers using a standardized protocol across all field centers. Experienced sonographers made measurements from digitized images using a standard software offline image analysis system (Digisonics Inc., Houston, TX). The echocardiography protocol at Year-25 has been previously published and followed existing American Society of Echocardiography guidelines for study acquisition and measurement. Quality-control and image analysis was performed at a core reading center (Johns Hopkins University, Baltimore, MD). Abnormal LV relaxation was defined as lateral tissue Doppler early diastolic tissue velocity (e') velocity ≤10 cm/s. Increased LV filling pressure was defined as early transmitial velocity (E/e') ratio ≥12 alone or the combination of E/e' ratio 8-12 and left atrial (LA) volume index ≥34 mL/m². LV mass was indexed to height²/³ and LA volume indexed to height. Speckle-tracking echocardiography images for myocardial strain and strain-rate measurements were analyzed in a 16-segment basis for LV mid-wall layer, using Wall Motion two-dimensional Tracking software (Toshiba Medical Systems). Three cardiac cycles from each view were recorded for offline analyses. Strain was calculated as the change in segment length relative to its end-diastolic length, and the peak systolic value was recorded.

**Statistical Analysis.** Linear regression models were used to quantify cross-sectional associations between exposure (continuous liver attenuation or presence of NAFLD) and outcome variables (echocardiographic parameters). Multinomial logistic regression models and logistic regression models were then used to assess the association of presence of NAFLD on categories of subclinical LV systolic and diastolic dysfunction, respectively. Covariates in the multivariable model were chosen a priori for clinical importance. Potential confounders included age, race, sex, study center, socioeconomic level, alcohol intake, physical activity score, and HF risk factors (e.g., diabetes status, systolic blood pressure [SBP], total cholesterol, high-density lipoprotein [HDL], and lipid and antihypertensive medication use). Potential effect modifiers were BMI and VAT. Pearson's correlation coefficients were computed between obesity measures and liver attenuation. Six models were fitted: Model 1 (base model): age, race, sex, study center, educational level, income level, alcohol intake, smoking status and physical activity score; Model 2: base model + HF risk factors; Model 3: base model + BMI; Model 4: base model + VAT; Model 5: base model + HF risk factors + BMI; and Model 6: base model + HF risk factors + VAT. Interaction terms were generated between...
NAFLD and race, sex, age, diabetes and hypertension (HTN) status, and levels of VAT volume or BMI in terms of e’ velocity, E/e’ ratio, or global longitudinal strain (GLS). A P value <0.05 was considered statistically significant. Analyses were performed using SAS software (version 9.4; SAS institute Inc., Cary, NC).

**Results**

**Clinical, Fat Distribution, and Metabolic Characteristics.** Clinical, demographic, metabolic, and laboratory characteristics of the 2,713 participants (58.8% female, 48.0% black), stratified by presence of NAFLD, are summarized in Table 1. NAFLD was present in 271 participants (prevalence = 10.0%). NAFLD participants were of similar age compared to non-NAFLD, but more likely to be male, white, and have MetS (Table 1). NAFLD participants were also more likely to be obese and have increased waist circumference, waist-to-hip ratio, and higher levels of CT-measured VAT volume (Table 1). When compared to non-NAFLD, NAFLD participants exhibited a higher prevalence of IR, as demonstrated by higher fasting insulin, glucose, and homeostatic model assessment of insulin resistance (HOMA-IR) scores, hypertriglyceridemia, and increased high sensitivity C-reactive protein (CRP) levels (Table 1).

**Association of NAFLD With Cardiac Structural and Functional Abnormalities: Unadjusted Analyses.** Compared to those without NAFLD, participants with fatty liver disease exhibited cardiac remodeling, manifested by higher LV mass index, LV relative wall thickness, LV end-diastolic volume, and LA volume index (Table 2). There was no significant difference in LV end-systolic volume. Among the systolic function parameters, circumferential strain and GLS, but not ejection fraction (EF), were significantly worse in NAFLD participants. Several diastolic function parameters were worse in NAFLD, including lower E/late (atrial) transmitral velocity (A) ratio and e’ velocity as well as a higher E/e’ ratio (Table 2). Cardiac output was also higher in NAFLD participants, though this effect was attenuated after accounting for body surface area.

Utilizing quartiles of GLS, we assessed differences in severity of subclinical systolic dysfunction between NAFLD and non-NAFLD participants (see Fig. 2). Despite a normal EF in both groups (Table 2), NAFLD participants were more likely to have significant subclinical systolic impairment on speckle-tracked imaging than non-NAFLD (P < 0.001 for trend). Similarly, compared to non-NAFLD, NAFLD participants were more likely to have subclinical diastolic dysfunction demonstrated by abnormal LV relaxation (34.6% vs. 23.6%; P < 0.0001) and increased LV filling pressures (33.3% vs. 23.7%; P < 0.001; see Fig. 3).

**Multivariable Analyses.** In multivariable linear regression analyses adjusted for demographics and health behaviors, the presence of NAFLD remained associated with worse GLS (Table 3; P < 0.0001). This association remained significant when adjusted for HF risk factors or measures of adiposity, including either BMI or VAT. However, the association between NAFLD and GLS was attenuated in the fully adjusted models with both HF risk factors and measures of adiposity. Likewise, NAFLD remained independently associated with significant impairment (quartile 1) in GLS when adjusted for demographics and health behaviors (odds ratio [OR]: 3.40; 95% confidence interval [CI]: 2.10, 5.48); the association persisted even after adjusting for traditional HF risk factors or measures of adiposity, including VAT. However, this association was attenuated when adiposity measures were added to the HF risk factor model (Table 4). NAFLD was also associated with several markers of diastolic dysfunction, including e’ velocity, E/A, and E/e’ ratio (a marker of LV filling pressure) when adjusted for demographics and health behaviors (Tables 3 and 4). These associations persisted in subsequent models after adjustment for BMI (Tables 3 and 4). However, only e’ velocity and E/e’ ratio remained significant after adjustment for VAT. In fully adjusted models for markers of adiposity, there was a trend toward a significant association only between NAFLD and e’ velocity, which is a marker of impaired cardiac relaxation (P = 0.05; Table 3). NAFLD was also independently associated with increased LV mass index, LV end-diastolic volume, and LA volume index when adjusted for demographics and health behaviors; however, these associations were attenuated after adjustment for HF risk factors. NAFLD was independently associated with cardiac output when adjusted for HF risk factors or BMI, though VAT attenuated this effect (Table 3). No significant interactions between NAFLD and sex, race, diabetes, or HTN status in association with markers of subclinical myocardial dysfunction were observed. However, there was an interaction between NAFLD and age, wherein younger (age range: 42-50 years) NAFLD participants were more likely to have impaired GLS (β = −0.76; standard error [SE] = 0.26; P = 0.003) and lower e’ velocity (β = −0.57; SE = 0.22; P = 0.01) than older (age, 51-59 years) NAFLD participants. Whereas the interaction term for NAFLD and age was statistically significant, stratified analysis of the association between NAFLD and measures of subclinical myocardial dysfunction in
Table 1. Characteristics of the Overall Study Sample and Participants With and Without NAFLD, the CARDIA Study, Year-25 Examination (2010-2011)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Sample (n = 2,713)</th>
<th>No NAFLD (n = 2,442)</th>
<th>NAFLD (n = 271)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50.1 ± 3.6</td>
<td>50.1 ± 3.6</td>
<td>50.5 ± 3.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Women</td>
<td>1,595 (58.8)</td>
<td>1,472 (60.3)</td>
<td>123 (45.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Menopause status - Yes</td>
<td>657 (41.6)</td>
<td>599 (41.1)</td>
<td>58 (47.9)</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.4</td>
<td>30.4</td>
<td>30.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>118.5</td>
<td>118.5</td>
<td>118.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>193.0 ± 36.5</td>
<td>193.1 ± 36.4</td>
<td>191.6 ± 37.7</td>
<td>0.50</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>112.7 ± 85.9</td>
<td>110.6 ± 85.7</td>
<td>106.6 ± 85.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9 ± 0.4</td>
<td>0.9 ± 0.4</td>
<td>0.9 ± 0.2</td>
<td>0.43</td>
</tr>
<tr>
<td>Log hsCRP</td>
<td>0.4 ± 1.2</td>
<td>0.4 ± 1.2</td>
<td>0.4 ± 1.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>NAFLD = liver attenuation ≤40 HU.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Results are expressed as mean ± standard deviation (SD) or number (%); t test for continuous variables, chi-square test, or Fischer's exact test for categorical variables for the difference between NAFLD and no NAFLD.</td>
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<tr>
<td>†Defined using the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) criteria.</td>
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</tr>
<tr>
<td>Abbreviations: SAT, subcutaneous adipose tissue; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.</td>
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</table>

Younger and older participants indicated that younger NAFLD participants had more severely impaired GLS and lower $e'$ velocity than older participants, but the direction of the association was the same regardless of age. Not surprisingly, there was an inverse correlation between BMI and liver attenuation ($r = -0.39; P < 0.0001$) and VAT and liver attenuation ($r = -0.54; P < 0.0001$). However, the variance inflation factors...
were <2 for all model covariates, suggesting that multicollinearity did not interfere with model fit. In addition, there was no significant interaction between NAFLD and levels of VAT volume or BMI in terms of e' velocity, E/e' ratio, or GLS. In sensitivity analyses, all findings remained consistent even when the cutpoint for the definition of NAFLD was increased to ≤40 HU (consistent with a liver/spleen ratio <1.0; data not shown) and when continuous liver attenuation was used (Supporting Table 1).

**Discussion**

In a large, population-based, cross-sectional study of both black and white middle-aged adults with NAFLD, we have shown that NAFLD is associated with both subclinical cardiac remodeling and systolic and diastolic function independent of traditional HF risk factors or markers of adiposity. In addition, to the best of our knowledge, this is the first study to also consider the effect of VAT, a potential confounder of the association...
Table 3. Linear Regression Analysis for the Association of NAFLD with Continuous Markers of Subclinical Myocardial Dysfunction, the CARDIA Study, 2010-2011

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>β (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Base Model*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Base + HF Risk Factors†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Base + BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Base + VAT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Base + HF Risk Factors + BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Base + VAT + BMI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac dimensions</th>
<th>Model 1, Base Model*</th>
<th>Model 2, Base + HF Risk Factors†</th>
<th>Model 3, Base + BMI</th>
<th>Model 4, Base + VAT</th>
<th>Model 5, Base + HF Risk Factors + BMI</th>
<th>Model 6, Base + VAT + BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index</td>
<td>5.8 (0.8)</td>
<td>&lt;0.0001 (0.0094)</td>
<td>0.0004 (0.028)</td>
<td>0.0005 (0.0096)</td>
<td>0.0004 (0.028)</td>
<td>0.0005 (0.0096)</td>
</tr>
<tr>
<td>LV end-diastolic volume</td>
<td>-1.9 (1.8)</td>
<td>0.08 (0.7)</td>
<td>0.04 (0.82)</td>
<td>0.04 (0.82)</td>
<td>0.04 (0.82)</td>
<td>0.04 (0.82)</td>
</tr>
<tr>
<td>Left atrial volume index</td>
<td>1.9 (0.68)</td>
<td>0.064 (0.06)</td>
<td>0.004 (0.026)</td>
<td>0.004 (0.026)</td>
<td>0.004 (0.026)</td>
<td>0.004 (0.026)</td>
</tr>
<tr>
<td>LV systolic myocardial function</td>
<td>-0.93 (0.16)</td>
<td>&lt;0.0001 (0.0094)</td>
<td>0.0001 (0.028)</td>
<td>0.0001 (0.028)</td>
<td>0.0001 (0.028)</td>
<td>0.0001 (0.028)</td>
</tr>
<tr>
<td>LV diastolic myocardial function</td>
<td>0.03 (0.2)</td>
<td>0.006 (0.026)</td>
<td>0.06 (0.36)</td>
<td>0.06 (0.36)</td>
<td>0.06 (0.36)</td>
<td>0.06 (0.36)</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.9 (0.68)</td>
<td>0.02 (0.02)</td>
<td>0.01 (0.04)</td>
<td>0.01 (0.04)</td>
<td>0.01 (0.04)</td>
<td>0.01 (0.04)</td>
</tr>
<tr>
<td>E/e' ratio</td>
<td>0.93 (0.16)</td>
<td>&lt;0.0001 (0.0094)</td>
<td>0.0001 (0.028)</td>
<td>0.0001 (0.028)</td>
<td>0.0001 (0.028)</td>
<td>0.0001 (0.028)</td>
</tr>
<tr>
<td>Lateral tissue Doppler e' velocity</td>
<td>-0.77 (0.14)</td>
<td>&lt;0.0001 (0.0094)</td>
<td>0.0001 (0.028)</td>
<td>0.0001 (0.028)</td>
<td>0.0001 (0.028)</td>
<td>0.0001 (0.028)</td>
</tr>
</tbody>
</table>

*Cardiac dimensions: Indexed to height; LV mass index = LV mass index/height^4. **HF risk factors: SBP, antihypertensive medication use, antihyperlipidemic medication use, total cholesterol, HDL cholesterol, diabetes status, and glomerular filtration rate.†BMI = body mass index. ‡Indexed to height; VAT = visceral adipose tissue.§Indexed to height. NAFLD is defined as CT liver attenuation/C20 HU.

NAFLD is associated with lower early diastolic relaxation (e') tissue velocity, lower E/A ratio, and higher estimated LV filling pressures (E/e' ratio), thus implying the presence of underlying subclinical diastolic dysfunction. Moreover, using speckle-tracking echocardiography, we also found that participants with NAFLD had reduced longitudinal LV systolic function, despite having a normal EF. A major finding of our study is that NAFLD is associated with the aforementioned echocardiographic features of subclinical LV remodeling and early LV diastolic and systolic dysfunction independent of several metabolic variables, including traditional HF risk factors and obesity (as measured by BMI). It is well established that obesity (e.g., BMI) is closely related to HF risk factors. Therefore, when BMI is added to the model with HF risk factors, we hypothesize that the attenuated findings are likely owing to overfitting and overadjustment for the effects of BMI, which may, in fact, lie in the causal pathway between NAFLD and subclinical myocardial dysfunction. In addition, the beta coefficients in the models with BMI alone or with HF risk factors alone are very similar, suggesting that obesity may account for a significant proportion of the observed association between NAFLD and subclinical myocardial dysfunction. Although there was some attenuation of associations by VAT, many of the associations between NAFLD and echocardiographic findings were still significant, suggesting that the correlation between NAFLD and VAT also does not fully explain our findings.

The current study adds to the available literature in that it used modern speckle-tracking techniques to assess early markers of systolic dysfunction in NAFLD participants. To date, only two small earlier studies25,27 with inconsistent findings have examined subclinical systolic dysfunction in NAFLD using speckle tracking. Our study is unique in that we used a population-based sample of otherwise healthy adults to analyze longitudinal strain among those with NAFLD. Myocardial strain is an important predictor of both morbidity29 and mortality30; therefore, identification of impaired early LV myocardial function by these techniques may help to identify NAFLD patients at increased cardiovascular risk.

Another novel finding in the current study is that NAFLD is independently associated with LA volume,
even when adjusted for traditional HF risk factors and BMI. LA volume is an indicator of both the severity and duration of LV diastolic dysfunction,\textsuperscript{31} and LA size has proven to be a powerful predictor of outcome in several disease entities, including MI,\textsuperscript{32} severe aortic valve stenosis,\textsuperscript{33} HF,\textsuperscript{34} and type 2 diabetes.\textsuperscript{35} LA volume may also be a better predictor of future symptomatic HF than the presence of diastolic dysfunction,\textsuperscript{35} and thus the presence of increased LA volume in NAFLD may serve as a marker of future HF events.

**Potential Pathophysiologic Mechanisms.** Several potential pathophysiologic mechanisms may explain the association between NAFLD and subclinical myocardial dysfunction (Fig. 4). We have demonstrated that NAFLD is related to increased body surface area and an increase in cardiac output and LV filling pressures, which we hypothesize that, over time, may lead to development of clinical HF. In addition, HS is associated with IR,\textsuperscript{12} myocardial lipid toxicity,\textsuperscript{36,37} and systemic release of several inflammatory mediators\textsuperscript{38} that can impair cardiac function.\textsuperscript{39,40} Previous studies have demonstrated that increased epicardial and intramyocardial fat content is associated with impaired cardiac metabolism.\textsuperscript{13,41} Although we did not analyze for cardiac ectopic fat in the current study, the attenuation of many of the observed effects by other metabolically active ectopic fat deposits (e.g., VAT) suggests that abnormal ectopic fat storage may be a marker of the cumulative effects of NAFLD and IR in the setting of pathological adiposity.\textsuperscript{42,43} We have shown that markers of obesity (especially VAT) and traditional HF risk factors attenuate, but do not completely account for, the association between NAFLD and subclinical myocardial dysfunction (Fig. 4). Ultimately, these mechanisms, paired with an increase in cardiac output, may lead to volume overload of a stiff LV and may result in the development of future clinical HF as LV filling pressures rise. Therefore, identification of HS in middle age, during which time HF risk factors (stage B) often transition to clinical (stage C) HF, may provide additional information about the pathogenesis of clinical HF development. Interestingly, several large, population-based cohort studies have demonstrated that moderately elevated levels of serum gamma-glutamyltransferase, which are possible markers of underlying NAFLD and atherosclerosis, are independently associated with an increased risk of incident HF.\textsuperscript{44-46} Thus, NAFLD may be an important future target in order to prevent and treat the increasing HF epidemic. Further prospective evaluations of these cross-sectional observed associations are needed.

**Strengths and Limitations.** The strengths of the present study include our large, well-characterized
population-based cohort of both whites and blacks, a NAFLD prevalence that is consistent with published population estimates, the use of tissue Doppler imaging and speckle-tracking analysis to assess subclinical myocardial dysfunction, and the measurement of a comprehensive set of metabolic covariates, particularly VAT. Thus, our findings are more generalizable to the U.S. population, compared to previously published findings in small, selected samples of NAFLD patients. Importantly, we excluded participants with known CLD and those with other potential reasons for increased hepatic fat, and thus were able to isolate those with the highest likelihood of having NAFLD in a subclinical state.

Some limitations warrant mention. Our findings are cross-sectional; therefore, neither temporal nor causal relationships can be inferred. CT is a relatively insensitive measure of hepatic fat, compared to hepatic triglyceride content measured by proton magnetic resonance spectroscopy (magnetic resonance spectroscopy), which may bias our results toward the null and underestimate the strength of the association between NAFLD and subclinical myocardial remodeling/dysfunction. Liver biopsy, the gold standard for diagnosis of NAFLD, is not feasible in epidemiological studies given the risks associated with the procedure. In addition, because contemporaneous laboratory data on hepatic function were not available to us in the present study, we excluded participants at high risk of CLD. Finally, there is no laboratory test for NAFLD; thus, documenting steatosis on imaging in the presence of risk factors after exclusion of other liver diseases makes the diagnosis. Therefore, the NAFLD definition used in this study is similar to what is used in clinical practice. Furthermore, serum aminotransferases are often normal despite the presence of liver injury in NAFLD. Thus, we doubt that hepatic function variables would have improved the classification of the NAFLD phenotype. We also acknowledge that several of the observed differences in echocardiographic parameters (e.g., E/A ratio 1.2 vs. 1.3), though statistically significant, may not represent a clinically significant difference. In addition, given the high correlation between markers of obesity and NAFLD, we chose to show the differential effects of traditional HF risk factors and markers of obesity on associations in separate models. Thus, our findings illuminate potential pathophysiologic mechanisms of the association between NAFLD and clinical HF and do not demonstrate a direct link to clinical HF. Future prospective study to determine the impact of NAFLD on the future development of clinical HF is needed.

In conclusion, NAFLD is independently associated with subclinical myocardial remodeling and dysfunction independent of established HF risk factors, including obesity, dyslipidemia, HTN, and diabetes. Other ectopic fat deposits, such as visceral adipose tissue, likely moderate some of this observed association. NAFLD may play an important role in the development of HF, especially HF with preserved EF, and the association between NAFLD and subclinical myocardial dysfunction provides

![Fig. 4. Proposed pathophysiologic mechanisms for the relationship between NAFLD and subclinical myocardial dysfunction. NAFLD is related to increased body surface area with a resultant increase in cardiac output (CO) and LV filling pressures, which leads to the development of clinical HF. NAFLD is also associated with IR, myocardial lipid toxicity, and systemic inflammation that can impair cardiac function. Both obesity and traditional HF risk factors attenuate, but do not completely account for, the association between NAFLD and subclinical myocardial dysfunction, which, when coupled with an increase in CO in the setting of a stiff LV, leads to clinical HF. Dotted lines indicate that the direction of association is not clearly established. Abbreviation: CAD, coronary artery disease.](image)
pathophysiological insight into the potential link between NAFLD and HF.

Acknowledgment: The authors thank the participants of the CARDIA study for their long-term commitment and important contributions to the study.

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Supporting Information