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Non-alcoholic fatty liver disease and vascular function – a cross-sectional analysis in the Framingham Heart Study

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Abstract

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Objective—Patients with non-alcoholic fatty liver disease (NAFLD) have an increased risk of cardiovascular disease (CVD); however, it is not known if NAFLD contributes to CVD independent of established risk factors. We examined the association between NAFLD and vascular function.

Approach and Results—We conducted a cross-sectional study of 2,284 Framingham Heart Study participants without overt CVD who had liver fat attenuation measured on computed tomography and who had measurements of vascular function and covariates. We evaluated the association between NAFLD and vascular function using multivariable partial correlations adjusting for age, sex, cohort, smoking, diabetes, hyperlipidemia, hypertension, body mass index (BMI) and visceral adipose tissue (VAT). The prevalence of NAFLD in our sample (mean age 52 ± 12 years, 51.4% women) was 15.3%. In age-, sex- and cohort-adjusted analyses, greater liver fat was modestly associated with lower flow-mediated dilation ($r = -0.05$, $P=0.02$), lower peripheral arterial tonometry ratio ($r = -0.20$, $P<0.0001$), higher carotid-femoral pulse wave velocity ($r = 0.13$, $P<0.0001$) and higher mean arterial pressure ($r = 0.11$, $P<0.0001$). In multivariable-adjusted models, NAFLD remained associated with higher mean arterial pressure ($r=0.06$, $P=0.005$) and lower peripheral arterial tonometry ratio ($r= -0.12$, $P<0.0001$). The association between NAFLD and peripheral arterial tonometry ratio persisted after further adjustment for BMI and VAT.

Conclusions—For multiple measures of vascular function, the relation with NAFLD appeared largely determined by shared cardiometabolic risk factors. The persistent relation with reduced peripheral arterial tonometry response beyond established risk factors suggests that NAFLD may contribute to microvascular dysfunction.

Keywords

vascular endothelial dysfunction; computed tomography; microvascular; obesity; risk factors

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver condition in the United States with a general population prevalence of 20-40%.[1, 2] NAFLD is associated with insulin resistance, obesity, type 2 diabetes and dyslipidemia.[3-5] In addition to the risk for advanced liver disease from non-alcoholic steatohepatitis (NASH), NAFLD confers an increased risk of cardiovascular disease (CVD).[6, 7] It is not fully established whether NAFLD increases CVD-related morbidity or mortality independent of known cardiovascular risk factors.[8]

The mechanisms by which NAFLD may lead to increased CVD are not known.[9] NAFLD may lead to increased CVD by modifying traditional risk factors such as dyslipidemia and insulin resistance.[10-12] A leading hypothesis is that hepatic steatosis may lead to the production of proinflammatory cytokines, which accelerate atherosclerosis and lead to progressive endothelial dysfunction.[6, 13, 14] Indeed, NAFLD is associated with an increased C-reactive protein, a marker of systemic inflammation.[15] Vascular endothelial dysfunction occurs early in the atherosclerosis process.[16] Non-invasive measures of endothelial function and arterial stiffness such as brachial artery flow-mediated dilation (FMD), fingertip peripheral arterial tonometry (PAT) and arterial tonometry are associated with cardiovascular risk factors and with incident CVD.[16-20] There have been several studies on the association of NAFLD and various markers of vascular structure and function.[21-33] These studies have been limited by small sample sizes, lack of adequate control for known cardiovascular risk factors, limited evaluation of vascular function and use of clinical samples.[22-33]

Thus, the goal of our study was to determine the association between NAFLD, as defined by decreased liver attenuation on multi-detector computed tomography (CT), and vascular function as measured by brachial artery FMD, PAT and arterial tonometry in a large, unselected community-based cohort without apparent CVD. Additionally, we explored whether associations remained after adjusting for known cardiovascular risk factors, body mass index (BMI) and visceral adipose tissue (VAT).

Materials and Methods

Materials and methods are available in the online-only Data Supplement.

Results

Study sample characteristics

Participant characteristics and mean values for vascular function measures for those with and without NAFLD are summarized in Table 1. Overall, 15.3% of the sample had a LPR ≤ 0.33, consistent with NAFLD.

Correlations between liver attenuation and vascular function measures

In minimally adjusted models, liver attenuation was significantly correlated with all vascular function measures, except for hyperemic mean flow velocity and forward wave amplitude (Table 2). With more liver fat (lower LPR), the response to ischemia as measured by FMD was lower, which is consistent with conduit vessel dysfunction. More liver fat was also associated with a lower PAT ratio, which is consistent with small vessel dysfunction. For the measures of arterial stiffness, more liver fat was associated with a higher CFPWV, which is consistent with greater arterial stiffness.

Multivariable-adjusted partial correlations for NAFLD with vascular function measures

In the multivariable-adjusted model, NAFLD (LPR ≤ 0.33) was positively associated with mean arterial pressure (MAP) (r=0.06, P=0.005) and inversely associated with the PAT ratio (r= −0.12, P<0.0001) (Table 3). After BMI was added to the multivariable model, the correlation between NAFLD (LPR ≤ 0.33) and MAP was no longer statistically significant (r=0.03, P=0.20). NAFLD (LPR ≤ 0.33) was also positively associated with CFPWV in the multivariable adjusted model (r=0.05, P=0.03); however, when this model was also adjusted for MAP the correlation was no longer statistically significant (r=0.02, P=0.29). The correlation between NAFLD (LPR ≤ 0.33) and the PAT ratio remained statistically significant after additionally adjusting for BMI (r=−0.09, P=0.0005) and VAT (r=−0.08, P=0.004) (Table 3). NAFLD (LPR ≤ 0.33) also was associated with higher baseline brachial artery diameter (multivariable model 1 only), baseline brachial artery mean flow velocity and baseline peripheral artery pulse amplitude (Supplementary Table II). When we evaluated LPR as a continuous variable, results were largely similar. (Table 3). The variance inflation factor was < 1.3 for each of these associations, suggesting the lack of severe multi-collinearity.

PAT ratio according to the presence of NAFLD overall and across BMI categories

The least-square means for the PAT ratio according to the presence of NAFLD overall and by BMI category are shown in Figure 1. Overall, the PAT ratio was lower among participants with NAFLD compared to those without NAFLD (p< 0.0001). In the overweight BMI category, the PAT ratio in participants with NAFLD was lower compared to those without NAFLD (p=0.0006), which is consistent with small vessel dysfunction. In the normal weight and obese BMI categories, the findings are in a similar direction; however, not statistically significant (PAT ratio normal weight NAFLD vs non-NAFLD p=0.26; PAT ratio obese NAFLD vs non-NAFLD p=0.06).

PAT ratio according to presence of NAFLD and CRP above and below median

The least-square means for the PAT ratio according to the presence of NAFLD and CRP above and below the median value are shown in Supplementary Figure I. Participants with NAFLD and either CRP < median or CRP ≥ median had a significantly lower PAT ratio compared to those without NAFLD and CRP < median (p=0.008 and p<0.0001 respectively). Among those with NAFLD, there was no difference in the PAT ratio in those with CRP > median vs CRP ≤ median (p=0.99).

PAT ratio according to presence of NAFLD and normal or elevated LFTs

The lease-square means for the PAT ratio according to the presence of NAFLD and elevated LFTs are shown in Supplementary Figure II. Participants with NAFLD and either normal or elevated LFTs had a significantly lower PAT ratio compared to those without NAFLD and normal LFTs (p=0.005 and p=0.0003 respectively). Among those with NAFLD, there was a trend towards a lower PAT ratio among those with elevated LFTs compared to those with normal LFTs; however, this did not meet statistical significance (p=0.41).

Sex interactions

In multivariable models of the main outcome measures, there was no evidence of effect modification by sex (p value range 0.16-0.90).

Analysis limited to the Third-Generation Cohort

In a secondary analysis limited to participants in the Third-Generation Cohort who had all vascular function measurements and the multi-detector CT scans at the same study visit, the results were not substantively changed (Supplementary Table III).

Analysis limited to the participants with all three vascular measures

In a secondary analysis limited to participants who had all three vascular measures (n=1005), the results were not substantively changed (Supplementary Table IV).

Discussion

In this large (n=2284) community-based cohort of participants without apparent CVD, we observed modest associations between lower liver attenuation (more liver fat) and FMD, a measure of conduit artery vasodilator function; PAT ratio, a measure of microvascular function; MAP, a measure of systemic perfusion; and CFPWV, a measure of arterial stiffness. The associations of NAFLD with conduit artery function and arterial stiffness were attenuated and no longer significant after adjusting for CVD risk factors. However, NAFLD remained correlated with measures of microvascular dysfunction including PAT ratio, baseline brachial artery mean flow velocity and baseline peripheral artery pulse amplitude even in models adjusted for CVD risk factors and adiposity measures. These findings are consistent with a potential association between NAFLD and microvascular dysfunction.

We advance the prior literature by evaluating microvascular dysfunction in NAFLD as measured by PAT. Although both markers of vasodilator function, brachial and digital measures of vasodilation evaluate distinct vascular beds and prior work suggests they reflect distinct aspects of vascular function.[34-36] We have previously demonstrated differences in the risk factors associated with brachial hyperemia and PAT with low digital vascular function being associated with metabolic risk factors including BMI, cholesterol and the presence of diabetes.[34, 37] Relevant to NAFLD, one prior selected study of patients with obstructive sleep apnea identified an association between hepatic steatosis and lower PAT.[38] The current investigation demonstrates, in a large community-based sample, an association between PAT ratio and NAFLD after adjusting for cardiovascular and metabolic risk factors. Further, across categories of obesity, the presence of NAFLD was associated with lower PAT hyperemic response. High baseline brachial flow is also gaining appreciation as a metabolic-disease associated vascular alteration.[39] In the present study, we observed higher resting flow velocity in participants with NAFLD that may contribute to microvascular damage. These results emphasize the association of NAFLD with abnormalities in the microcirculation.

Previous smaller studies have evaluated the relation of NAFLD with several individual measures of vascular function. In small, clinically selected samples, patients with biopsy proven NAFLD had conduit artery dysfunction, as measured by brachial artery FMD, compared to age- and sex-matched controls.[24, 26] The association of clinical NAFLD with reduced FMD persisted when accounting for a limited set of metabolic risk factors.[24, 28] NAFLD determined by ultrasound also has been associated with lower endothelium-dependent dilation in clinical samples.[22, 25, 31] Similarly, one study showed higher aortic stiffness in patients with biopsy-proven NAFLD.[28] In community-based cohorts, an association was observed between sonographically defined NAFLD and higher arterial stiffness measured using a global stiffness measures, brachial-ankle pulse wave velocity, and carotid-femoral pulse wave velocity.[28, 29, 32] However, in a study of adolescents with ultrasound defined NAFLD, the association between NAFLD and higher arterial stiffness was limited to participants with high risk metabolic features including greater waist circumference, triglycerides, insulin, systolic blood pressure and lower high-density lipoprotein.[27] Thus, whether NAFLD is associated with abnormal vascular function beyond the associated cardiometabolic risk factors remained unclear.

In this study, we had the opportunity to evaluate multiple measures reflecting distinct aspects of vascular health in a community-based sample with a comprehensive assessment of cardiometabolic risk factors. In contrast to prior work, we observed that the NAFLD was no longer associated with conduit artery function or aortic stiffness after adjusting for concurrent risk factors. Thus, our findings suggest that the risk factors that cluster with NAFLD account for the observed vascular dysfunction, particularly in the conduit and large arteries. There are several possible explanations for these apparently discrepant results. First of all, several of the prior studies utilized hospital-based patient samples, which may have a higher prevalence of co-morbid conditions that contribute to conduit artery dysfunction and arterial stiffness compared to our study in a community-based sample. It is also possible that large artery dysfunction and arterial stiffness occur later in the pathogenesis of NAFLD. In addition, the large sample size and detailed assessment of cardiovascular risk factors including adiposity measures allowed for a more complete adjustment for potential confounding in our study. Thus, NAFLD may be associated with vascular dysfunction through processes that also drive the occurrence of traditional risk factors including dyslipidemia, hyperglycemia, insulin resistance, and blood pressure.

Several potential factors may underlie the association of NAFLD with vascular dysfunction. Liver fat accumulation occurs in a complex of metabolic disturbances including abdominal obesity and dyslipidemia.[4] Thus, isolating the association of fatty liver from the coexistent metabolic disruptions is not straightforward. Endothelial dysfunction may also contribute to the development of fatty liver.[33] It has been proposed that the liver is both exposed to an abnormal metabolic environment and a source of substances that promote vascular damage.[13] Fatty liver has been associated with increased pro-inflammatory cytokine production and heightened oxidative stress.[13] Thus, reduced vascular function associated with NAFLD may reflect systemic inflammation. Both conduit and small vessel flow-mediated dilation depend on endothelial production of nitric oxide that may be reduced in the setting of inflammation.[40] However, it may be that small vessel vasodilator responses have greater susceptibility to metabolic insults, including NAFLD, prior to the development of atherosclerotic disease.[17, 34] Further longitudinal studies are needed to define the precise mechanisms linking NAFLD to microvascular damage.

The major strengths of our investigation include our use of a large community-based sample that has not been selected for NAFLD and the detailed assessment of multiple measures of vascular function. In this well-characterized sample with a thorough assessment of covariates using standardized measurements, we are able to add to the current literature by adjusting for several important confounders in exploring the association with endothelial dysfunction and NAFLD in multivariable models.

There are a number of important limitations to our investigation that warrant mention. First, the cross-sectional design of this observational study precludes any inferences on causality or temporality. The FHS is largely Caucasian so results may not be generalizable to individuals of non-European ancestry. Additionally, we defined NAFLD based on CT imaging, which likely underrepresents the burden of NAFLD in the population, which may have led to non-differential misclassification biasing our results to the null.[41] Also, CT imaging cannot accurately detect steatohepatitis so we are unable to determine the association of vascular function and NAFLD disease severity. We also lack information about viral hepatitis status and other chronic liver conditions which can cause the appearance of liver fat on CT scan. However, these findings would likely lead to misclassification and would bias our findings towards the null. Thus, they are unlikely to account for our positive results. For the Offspring Cohort participants, there were temporal differences between the vascular measures and CT scans. However, in a sensitivity analysis limited to the Third Generation Cohort participants who had vascular measures and CT scans at the same study visit, our results were similar. Additionally, those participants with available PAT measurements were older and had more cardiometabolic risk factors compared to those with missing data. This may have led to a selection bias away from the null. However, when the analysis was repeated in participants who had all vascular measures, the results were largely unchanged. Overall, while statistically significant, the magnitude of the association between NAFLD and the PAT ratio is modest. Future longitudinal studies are necessary to explore the clinical significance of our findings.

We observed an association between NAFLD and markers of endothelial dysfunction and arterial stiffness. Future longitudinal studies are required to further explore the association between NAFLD and microvascular dysfunction and how this relates to cardiovascular risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
CVD	cardiovascular disease
FMD	flow-mediated dilation
PAT	peripheral arterial tonometry
CT	computed tonometry
BMI	body mass index
VAT	visceral adipose tissue
FHS	Framingham Heart Study

HU	Hounsfield Units
SAT	subcutaneous adipose tissue
LPR	liver phantom ratio
CFPWV	carotid-femoral pulse wave velocity
MAP	mean arterial pressure

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Significance

Patients with non-alcoholic fatty liver disease (NAFLD) are at risk for cardiovascular disease. We evaluated the association between NAFLD and multiple measures of vascular function in a large (n=2284) community-based cohort of participants without apparent CVD. Overall NAFLD is associated with multiple aspects of vascular function; however, this association is largely attributed to co-existing cardiometabolic risk factors. However, NAFLD remained correlated with measures of microvascular dysfunction in adjusted models. Future longitudinal studies should further explore the association between NAFLD and microvascular dysfunction and how this relates to cardiovascular risk.

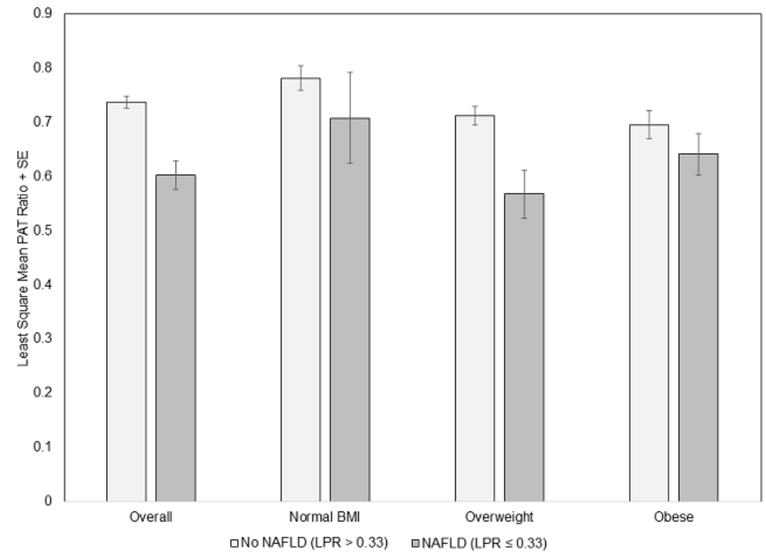

Figure 1. Bar chart depicting the multivariable adjusted least square means of peripheral arterial tone (PAT) ratio + standard error (SE) overall and by Body Mass Index (BMI) categories according to presence or absence of NAFLD

The BMI categories are defined as normal BMI (BMI < 25 kg/m^2), Overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2) and Obese (BMI ≥ 30 kg/m^2). No NAFLD represents a normal Liver Phantom Ratio (LPR) (LPR > 0.33) and NAFLD represents an abnormal LPR (LPR ≤ 0.33). Overall, PAT ratio NAFLD vs non-NAFLD p<0.0001;PAT ratio normal weight NAFLD vs non-NAFLD p=0.26; PAT ratio overweight NAFLD vs non-NAFLD p=0.0006; PAT ratio obese NAFLD vs non-NAFLD p=0.06.

Table 1

Participant characteristics, by presence of non-alcoholic fatty liver disease.

Clinical characteristics*	**NAFLD (LPR ≤ 0.33) (N = 350)**	**Non-NAFLD (LPR > 0.33) (N = 1934)**	**Total (N = 2284)**
Age (years)	54 ± 12	52 ± 12	52 ± 12
Women, N (%)	157 (44.9)	1017 (52.6)	1174 (51.4)
Offspring, N (%)	137 (39.1)	675 (34.9)	812 (35.6)
Current smoking, N (%)	35 (10.0)	208 (10.8)	243 (10.6)
Heart rate (beats/min)	64 ± 10	61 ± 10	62 ± 10
Total/high density lipoprotein cholesterol	4.46 ± 1.58	3.66 ± 1.19	3.78 ± 1.29
Triglycerides (mg/dl)	170 ± 124	107 ± 62	116 ± 79
Fasting glucose (mg/dl)	108 ± 27	97 ± 18	99 ± 20
Mean arterial pressure (mm Hg)	94 ± 9	90 ± 10	90 ± 10
Postmenopausal, N (%)	100 (63.7)	516 (50.7)	616 (52.5)
Hormone replacement therapy, N (%)	14 (8.9)	96 (9.4)	110 (9.4)
Diabetes, N (%)	52 (14.9)	71 (3.7)	123 (5.4)
Hypertension treatment, N (%)	126 (36.0)	355 (18.4)	481 (21.1)
Lipid lowering treatment, N (%)	92 (26.3)	336 (17.4)	428 (18.7)
C-reactive protein (mg/L)**	2.57 (1.16,4.76)	0.98 (0.46,2.25)	1.12 (0.50,0.27)
Alanine Aminotransferase (U/L)	36.4 ± 27.6	24.5 ± 16.6	26.3 ± 19.2
Aspartate Aminotransferase (U/L)	28.6 ± 24.6	23.4 ± 9.6	24.2 ± 13.2
Adiposity measures			
Body mass index, kg/m^2	31.0 ± 5.5	26.6 ± 4.7	27.3 ± 5.1
Waist circumference (cm)	106 ± 14	94 ± 13	96 ± 14
Visceral adipose tissue (cm^3)	2488 ± 993	1501 ± 876	1652 ± 963
Liver phantom ratio	0.27 ± 0.06	0.38 ± 0.02	0.36 ± 0.05
Vascular measures			
Brachial artery measures			
Baseline brachial artery diameter (mm)	4.47 ± 0.86	4.14 ± 0.83	4.19 ± 0.85
Flow mediated dilation (%)	4.06 ± 3.65	4.81 ± 3.56	4.69 ± 3.59
Baseline mean flow velocity (cm/s)	9.41 ± 5.03	7.12 ± 4.28	7.49 ± 4.49
Hyperemic mean flow velocity (cm/s)	56 ± 20	59 ± 20	58 ± 20
Peripheral Arterial Tonometry measures			
Baseline mean amplitude (unitless)	6.1 ± 0.8	5.6 ± 0.9	5.7 ± 0.9
Peripheral arterial tone ratio† (unitless)	0.53 ± 0.36	0.75 ± 0.41	0.72 ± 0.41
Arterial Tonometry measures			
Carotid-femoral pulse wave velocity (ms/mm)	9.0 ± 2.7	8.1 ± 2.6	8.3 ± 2.6
−1000/Carotid-femoral pulse wave velocity (ms/mm)	−119 ± 28	−131 ± 29	−129 ± 30
Forward wave amplitude (mm Hg)	50 ± 14	48 ± 14	48 ± 14

Clinical characteristics*	NAFLD (LPR ≤ 0.33) (N = 350)	Non-NAFLD (LPR > 0.33) (N = 1934)	Total (N = 2284)
Augmentation Index (%)	11.3 ± 12.8	11.6 ± 12.1	11.6 ± 12.2
Mean arterial pressure (mm Hg)	97 ± 10	93 ± 11	93 ± 11

Continuous variables expressed as mean ± sd and categorical variables as n (%) unless noted. NAFLD, Non-alcoholic fatty liver disease; LPR, liver phantom ratio; LFT, liver function test.

[*] Clinical characteristics were assessed for the Offspring participants at examination 7. Adiposity measures were assessed for the Offspring participants between examination 7 and 8. Peripheral arterial tonometry and arterial tonometry variables were assessed for the Offspring participants at examination 8. Third-generation participants had clinical characteristics and all vascular function measurements assessed at examination 1.

[**] Values represent median (Interquartile range)

[†] Peripheral artery tone measures are natural logarithm transformed.

Table 2

Age-, sex-, cohort-adjusted associations between liver phantom ratio (LPR) and vascular function measures.

Vascular function measures	**−LPR***		
	N	**r**	**P-value**
Brachial artery measures			
Flow-mediated dilation (%)	2061	−0.05	0.02
Hyperemic mean flow velocity (cm/s)	2061	−0.03	0.19
Peripheral Arterial Tonometry measures			
Peripheral arterial tone ratio† (unitless)	1393	−0.20	<0.0001
Arterial tonometry measures			
−1,000/Carotid-femoral pulse wave velocity (ms/mm)	2284	0.13	<0.0001
Forward-wave amplitude (mm Hg)	2284	0.02	0.27
Mean arterial pressure (mm Hg)	2284	0.1	<0.0001

*Data is modeled such that correlations are expressed per lower levels of LPR.

†Peripheral artery tonometry measures are natural logarithm transformed.

Table 3

Multivariable-adjusted* partial correlations for NAFLD as a dichotomous variable (LPR > 0.33 vs. LPR ≤ 0.33) or a continuous variable with vascular function measures.

Vascular function measures		**Model 1: MV* adjusted**		**Model 2: Model 1 + BMI adjusted**		**Model 3: Model 2 + VAT adjusted**	
	N	**r**	**P-Value**	**r**	**P-Value**	**r**	**P-Value**
Dichotomous fatty liver							
Brachial artery measures†							
Flow-mediated dilation (%)	2061	−0.02	0.30	−0.01	0.61	−0.01	0.66
Peripheral Arterial Tonometry measures							
Peripheral arterial tone ratio (unitless)	1393	−0.12	<0.0001	−0.09	0.0005	−0.08	0.004
Arterial tonometry measures							
−1,000/Carotid-femoral pulse wave velocity (ms/mm) †	2284	0.05	0.03	0.03	0.23	0.007	0.73
−1,000/Carotid-femoral pulse wave velocity (ms/mm)	2284	0.02	0.29	0.01	0.55	−0.004	0.85
Mean arterial pressure (mm Hg)	2284	0.06	0.005	0.03	0.20	0.02	0.26
Mean arterial pressure (mm Hg) ‡	2284	0.05	0.03	0.02	0.37	0.02	0.28
Continuous fatty liver							
Brachial artery measures†							
Flow-mediated dilation (%)	2061	−0.04	0.06	−0.03	0.15	−0.03	0.17
Peripheral Arterial Tonometry measures							
Peripheral arterial tone ratio (unitless)	1393	−0.13	<0.0001	−0.10	0.0001	−0.08	0.002
Arterial tonometry measures							
−1,000/Carotid-femoral pulse wave velocity (ms/mm) †	2284	0.03	0.12	0.01	0.52	−0.009	0.66
−1,000/Carotid-femoral pulse wave velocity (ms/mm)	2284	0.02	0.31	0.01	0.57	−0.01	0.68
Mean arterial pressure (mm Hg)	2284	0.02	0.28	−0.01	0.68	−0.01	0.51
Mean arterial pressure (mm Hg) ‡	2284	0.01	0.61	−0.02	0.47	−0.01	0.60

NAFLD, Non-alcoholic fatty liver disease; BMI, body mass index; VAT, visceral adipose tissue.

*Multivariable models adjusted for age, sex, cohort, smoking, mean arterial pressure (not included in models with mean arterial pressure or CFPWV as dependent variable, unless noted), heart rate, walk test (before, only for brachial measures†), total/high density lipoprotein cholesterol, triglycerides, fasting glucose level, menopause, hormone replacement therapy, diabetes, hypertension treatment and lipid lowering treatment.

†not adjusted on mean arterial pressure;

‡additional adjusted on carotid femoral pulse wave velocity.