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# Bidirectional relationship between fatty liver and cardiovascular disease risk factors

**Jiantao Ma**[1,2], **Shih-Jen Hwang**[1,2], **Alison Pedley**[1,2], **Joseph M. Massaro**[1,2,3], **Udo Hoffmann**[4], **Raymond T. Chung**[5], **Emelia J. Benjamin**[1,6,7], **Daniel Levy**[1,2], **Caroline S. Fox**[1,2,8], and **Michelle T. Long**[9]

[1] The Framingham Heart Study, Division of Intramural Research, National Heart, Lung, and Blood Institute, Framingham, Massachusetts

[2] Population Sciences Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, Framingham, Massachusetts

[3] Department of Mathematics and Statistics, Boston University, Boston, Massachusetts

[4] Radiology Department, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

[5] Liver Center, Gastrointestinal Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

[6] Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts

[7] Evans Department of Medicine, Whitaker Cardiovascular Institute and Cardiology Section, Boston University School of Medicine, Boston, Massachusetts

[8] Division of Endocrinology and Metabolism, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

[9] Division of Gastroenterology, Evans Department of Medicine, Boston University School of Medicine, Boston, Massachusetts

## Abstract

**Correspondence:** Michelle T. Long, MD, Boston University School of Medicine, Section of Gastroenterology, 85 East Concord Street 7th Floor, Boston MA 02118, mtlong@bu.edu, Tel: (617) 638-8392, Fax: (617) 638-6529.



**Disclosure.** None

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**Author contributions**: JM and MTL designed the analysis; JM analyzed the data and wrote the manuscript; SJH, AP, and JMM provided statistical support; DL, RTC, UH, EJB, CSF, and MTL provided critical editorial comments; MTL had primary responsibility for the final content. All authors read and approved the final manuscript.

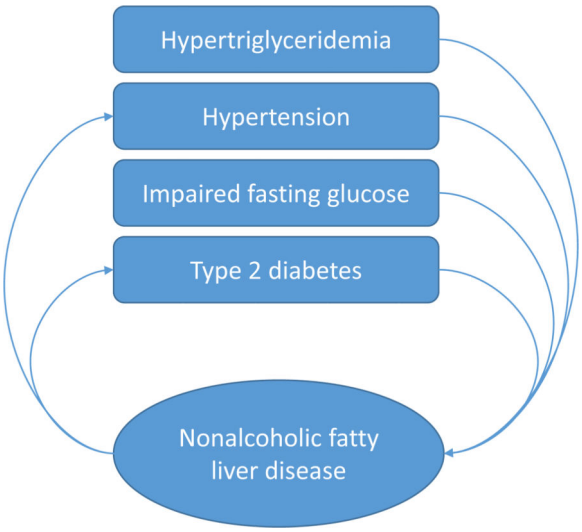
**Background & Aims—**The relations of non-alcoholic fatty liver disease to cardiovascular disease (CVD) risk factors are not fully understood. The objective of our study is to explore the bi-directional relationships of fatty liver to CVD risk factors.

**Methods—**We prospectively evaluated whether liver fat predicted the development of CVD risk factors and whether CVD risk factors predicted new onset fatty liver during 6 years of follow up in middle- to older-aged Framingham Heart Study participants. We estimated liver fat using multi-detector computed tomography.

**Results—**We included 1,051 participants (mean age 45 ± 6 years, 46% women). The prevalence of fatty liver was 18% at baseline. In participants without fatty liver at baseline, 101 participants developed incident fatty liver over approximately 6 years. Baseline liver fat (per standard deviation increase) was associated with increased odds of incident hypertension (OR 1.42; 95% CI 1.15-1.76; $p$=0.001) and incident type 2 diabetes (OR 1.43; 95% CI 1.09-1.88, $p$<0.001). In a parallel analysis, individuals with hypertension (OR 3.34; 95% CI 2.04-5.49), hypertriglyceridemia (OR 3.04; 95% CI:1.84-5.02), impaired fasting glucose (OR 2.92; 95% CI 1.76-4.82), or type 2 diabetes (OR 4.15; 95% CI 1.19-14.46) at baseline had higher odds of incident fatty liver compared to individuals without those conditions (all $p$<0.03). In both analyses, the observed associations remained similar after additional adjustments for measures of adiposity.

**Conclusions—**The present study demonstrated bi-directional relationships between fatty liver and CVD risk factors among middle- to older-aged Framingham Heart Study participants.

## Graphical abstract




### Keywords

Nonalcoholic fatty liver; type 2 diabetes; hypertension; hypertriglyceridemia; impaired fasting glucose; metabolic syndrome; cardiovascular disease risk factors

## Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most common liver disease in the US, affecting an estimated 20-30% of the adult population [1]. It is expected that the prevalence of NAFLD will continue to increase due to the rising incidence of obesity [2]. Hepatic steatosis or fatty liver is the defining characteristic of NAFLD [3, 4], which can be assessed by either imaging or histology [1]. Several observational studies have demonstrated an association between NAFLD and risk for cardiovascular disease (CVD) [5-7].

The increased risk for CVD in patients with NAFLD may be due to their increased burden of cardiometabolic metabolic risk factors or because NAFLD contributes directly to CVD risk. We have previously demonstrated that NAFLD is cross-sectionally associated with CVD risk factors including higher mean blood pressure, adverse lipid profiles, impaired fasting glucose, as well as higher prevalence of metabolic syndrome, hypertension, and type 2 diabetes, even after adjusting for visceral adipose tissue (VAT) [8]. However, prior studies have not fully examined the prospective associations between NAFLD and CVD risk factors. It remains uncertain whether NAFLD precedes or develops after adverse CVD risk factors.

Thus, the objective of our study is to determine the bi-directional relationships between fatty liver and CVD risk factors, i.e., if liver fat predicts the incidence of CVD risk factors or if CVD risk factors herald the accumulation of fat in the liver. Additionally, we examined if the hypothesized bidirectional relationships are beyond that is accounted for by generalized or visceral adiposity.

## Methods

### Study sample

We studied the Third Generation cohort of the Framingham Heart Study, which has been described elsewhere [9]. Briefly, 4,095 participants attended the first examination between 2002 and 2005. Among these participants, 3,411 also attended the second examination between 2008 and 2011. The mean interval between the two examinations was 6.2 years. We obtained liver fat measurements from 2,066 participants at baseline and from 1,194 participants at both examinations. Participants were excluded if they had a history of myocardial infarction or stroke, cancer (excluding non-melanoma skin cancer), bariatric surgery, or heavy alcohol consumption (>14 drinks/week in women and >21 drinks/week in men) [1], or missing information on alcohol intake, smoking status, physical activity, BMI, or volume of VAT at baseline or follow-up (Figure 1). After initial exclusion, data collected from 1,051 participants and from 1,015 participants were available for the analysis of baseline liver fat and incident CVD risk factors and for the analysis of baseline CVD risk factors and incident fatty liver, respectively. In these analyses, participants were additionally excluded; however, the exclusion criteria and the number of excluded participants varied for different analyses. In the analysis of baseline liver fat and incident CVD risk factors, we additionally excluded any participant with prevalent CVD risk factors at baseline, missing CVD risk factors at either baseline or follow-up, or missing continuous CVD risk factors at baseline. In the analysis of baseline CVD risk factors and incident fatty liver, we excluded participants who had prevalent fatty liver at baseline and participants who had missing data

regarding baseline CVD risk factors. In analysis using baseline continuous CVD risk factors as exposure variables, we additionally excluded participants if they used medications related to CVD risk factors at baseline. All participants provided written informed consent and the Framingham Heart Study protocols and procedures were approved by the Institutional Review Board for Human Research at Boston University Medical Center.

### Liver fat and VAT assessment

We reported the protocols for assessing liver fat [10-12] and VAT [13, 14] elsewhere. Briefly, participants underwent an abdominal scan with multiple-detector computed tomography (MDCT) scanners (General Electric Health Care), an 8-slice scanner at baseline and a 64-slice scanner at follow-up. The mean Hounsfield unit from three regions in the liver was calculated, and the ratio of the mean Hounsfield unit of the liver to the Hounsfield unit of a calibration control (phantom) was multiplied by 100 to represent liver fat content [8]. A lower value of the liver-phantom ratio (LPR) represents more liver fat. Fatty liver was defined using the sex- and examination-specific $20^{th}$ percentiles in participants without myocardial infarction or stroke, cancer (excluding non-melanoma skin cancer), bariatric surgery, or heavy alcohol consumption, i.e., LPR ≤ 32.8 in men and ≤ 34.0 in women at baseline or ≤ 30.0 in men and ≤ 32.9 in women at follow-up. We also used LPR ≤ 33.0 to define fatty liver as we have previously validated [10, 15]. We estimated VAT volume using the same MDCT scans as previously described [13, 14]. The intra-class correlations were 0.99 for both liver fat and VAT volume readings.

### CVD risk factors assessment

Standard protocols were applied to measure systolic blood pressure (BP), diastolic BP, fasting serum triglycerides, high density lipoprotein cholesterol (HDLc), and fasting plasma glucose at both examinations [16]. We calculated systolic BP and diastolic BP as the mean of the clinic physician's two blood pressure measurements. We defined hypertension as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or the use of anti-hypertensive medications; hypertriglyceridemia as triglycerides ≥150 mg/dL; low-HDLc as HDLc <50 mg/dL for women or <40 mg/dL for men; type 2 diabetes as fasting glucose ≥126 mg/dL or the use of hypoglycemic medications; and impaired fasting glucose (IFG) as fasting glucose ≥100 to <126 mg/dL in the absence of treatment for type 2 diabetes. Metabolic syndrome was defined using adapted ATP III criteria [17].

### Anthropometry and Covariate Assessment

Body weight (rounded to the nearest ½ pound) was measured with light clothes. Standing height (rounded to the nearest ¼ inch) was measured using a vertical ruler. We calculated BMI as weight (kg) divided by height ($m^2$). Current smokers were determined if participants had smoked regularly in the past year before the examination. Physical activity level was estimated from a technician-administered questionnaire evaluating the intensity of the activity and time spent performing a specific activity in a typical day. Information regarding alcohol intake (beer, wine, and liquor) was obtained using a questionnaire administered face-to-face during the medical examination [18].

### Statistical analysis

The primary analysis had two parallel sections to examine the association of baseline fatty liver and incident CVD risk factors and the association of baseline CVD risk factors and incident fatty liver.

### Baseline liver fat and incident CVD risk factors

The outcomes in this analysis included incident metabolic syndrome, hypertension, low-HDLc, hypertriglyceridemia, IFG, and type 2 diabetes. Exposure variables were baseline liver fat (per standard deviation, i.e., 5 units, decrease of LPR) or fatty liver (based on the LPR cut-off). Multivariable logistic regression models were implemented with adjustment for five sets of covariates. The initial model adjusted for baseline age, sex, smoking status, physical activity level, alcohol intake, and systolic BP, diastolic BP, triglycerides, HDLc, or glucose at baseline as appropriate (e.g., glucose for incident IFG and type 2 diabetes, systolic BP and diastolic BP for incident hypertension, and all for incident metabolic syndrome). We additionally adjusted for baseline BMI or VAT in separate models. In addition, we examined whether change in liver fat (LPR) and change in BMI or change in VAT might confound the observed associations.

### Baseline CVD risk factors and incident fatty liver

The outcome was incident fatty liver. Exposure variables in this analysis included baseline continuous CVD risk factors: systolic BP, diastolic BP, triglycerides, HDLc, and glucose, and baseline dichotomous CVD risk factors: metabolic syndrome, hypertension, hypertriglyceridemia, low-HDLc, IFG, and type 2 diabetes. We performed multivariable logistic regression models and adjusted for the sequence of models as in the analysis for baseline liver fat and incident CVD risk factors, except we did not adjust for liver fat change.

In a secondary analysis, we analyzed an alternative definition for fatty liver, i.e., LPR ≤ 0.33, which we have previously used and validated [10, 15]. In the sensitivity analysis for baseline liver fat and incident CVD risk factors, we included 771 participants who had baseline liver fat measurement but without liver fat measurement at follow-up. We implemented the same additional exclusion criteria as in the primary analysis. Due to missing information, change in adiposity was not adjusted for in the sensitivity analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. All statistical analyses were conducted using SAS statistical software (version 9.3; SAS Institute, Cary, North Carolina). A two-tailed $P<0.05$ was considered statistically significant, unless otherwise specified.

## Results

### Baseline characteristics

Among 1,051 participants with baseline liver fat measurements (Table 1), 18% had fatty liver at baseline. In participants without fatty liver at baseline (841 out 1,015 participants), 12% (n=101) developed incident fatty liver (Table S1). Compared with those without fatty liver at baseline (Table 1), participants with fatty liver were older, had greater BMI and VAT volume, and more likely to have metabolic syndrome, hypertension, low-HDLc,

hypertriglyceridemia, IFG, and type 2 diabetes (all $p<0.05$). We observed similar results when comparing participants with and without incident fatty liver at follow-up (Table S1).

### Baseline fatty liver and incident CVD risk factors

As shown in Table 2, a one standard deviation increase of baseline liver fat was associated with a 42% increased odds of incident hypertension (OR 1.42, 95% CI: 1.15, 1.76, $p=0.001$), a 28% increased odds of IFG (OR 1.28; 95%CI: 1.03, 1.60, $p=0.03$), and a 43% increased odds of type 2 diabetes (OR 1.43; 95%CI: 1.09, 1.88, $p=0.01$). The association between baseline liver fat and incident hypertension and incident type 2 diabetes remained significant after adjustment for baseline BMI or baseline VAT, as well as after adjustment for liver fat change and BMI change or liver fat change and VAT change (all $p<0.05$).

Similarly, compared with those without fatty liver at baseline, participants with fatty liver had greater odds of incident hypertension (OR 1.79; 95% CI: 1.04, 3.06, $p=0.03$), IFG (OR 1.75; 95% CI: 1.03, 2.98, $p=0.04$), and type 2 diabetes (OR 2.75; 95% CI: 1.35, 5.61, $p=0.005$). After adjustment for baseline adiposity or change in adiposity, the association between baseline fatty liver and incident hypertension or IFG became non-significant (all $p>0.05$); however, the association between baseline fatty liver and incident type 2 diabetes persisted (all $p\leq0.02$). No association between baseline liver fat or fatty liver and incident metabolic syndrome, hypertriglyceridemia, or low-HDLc was observed (all $p>0.05$).

In the sensitivity analysis, which included an additional 771 participants with baseline liver fat assessment, we identified more incident cases of CVD risk factors during the 6 years of follow up (Table S2). The positive association between baseline liver and incident type 2 diabetes or incident hypertension persisted, except that the association between baseline liver fat and incident hypertension was not significant in the baseline VAT-adjusted model (OR 1.16; 95% CI: 0.97, 1.38, $p=0.10$).

### Baseline CVD risk factors and incident fatty liver

As shown in Table 3, greater systolic BP, diastolic BP, triglycerides (logged), and glucose were associated with increased odds of incident fatty liver (all $p\leq0.001$). These associations largely persisted after additional adjustment for baseline BMI, baseline VAT, change in BMI, or change in VAT, particularly the association between baseline DBP and incident fatty liver (all $p\leq0.002$) and between baseline glucose and incident fatty liver (all $p\leq0.01$).

As shown in Table 4, participants with baseline metabolic syndrome (OR 4.63; 95% CI: 2.87, 7.47), hypertension (OR 3.34; 95% CI, 2.04, 5.49), hypertriglyceridemia (OR 3.04; 95% CI: 1.84, 5.02), IFG (OR 2.92; 95% CI: 1.76, 4.82), or type 2 diabetes (OR 4.15; 95% CI: 1.19, 14.46) had greater odds of incident fatty liver compared to individuals without these conditions (all $p\leq0.03$). After additional adjustment for baseline adiposity and change in adiposity, the observed association remained similar (all $p\leq0.02$).

### Secondary analysis

In analyses using an alternative definition for fatty liver (i.e., LPR≤33.0), the observed association between liver fat and CVD risk factors was similar to that described above (data not shown).

## Discussion

In our community-based, prospective cohort study of middle-aged to older adults without high alcohol consumption or apparent CVD, we examined the bi-directional relations between liver fat and CVD risk factors during approximately 6 years of follow-up. We observed that, in one direction, CVD risk factors including metabolic syndrome, hypertension, hypertriglyceridemia, IFG, and type 2 diabetes at baseline were associated with an increased risk of developing fatty liver that persisted after adjustment for overall adiposity (BMI) or VAT. In the other direction, we observed that greater baseline liver fat was associated with a greater risk of incident hypertension and type 2 diabetes. Taken together, our data suggest bi-directional relationships between NAFLD and CVD risk factors.

It has been suggested that NAFLD should be regarded as a component of metabolic syndrome [19]. Many studies have reported a cross-sectional association between NAFLD and metabolic syndrome [8, 20, 21], as well as between NAFLD and the key components of metabolic syndrome, i.e., dyslipidemia, hypertension, and hyperglycemia [8, 22]. The longitudinal association of NAFLD with these metabolic disorders or CVD risk factors, however, has not been well examined.

Several systematic reviews and meta-analyses of prospective cohort studies suggested that NAFLD predicts incident type 2 diabetes [23-25]. However, the generalizability of these studies is limited by the fact that almost all of these study samples were in Asian populations. In a group of obese participants (54% black, 29% white, 17% Hispanic individuals), visceral fat rather than liver fat was associated with incident type 2 diabetes [26]. In addition, it has been postulated that a self-perpetuating cycle exists, i.e., NAFLD induces type 2 diabetes, which in turn promotes the progression of NAFLD [25]. However, to date, few studies have examined the bidirectional association between NAFLD and impaired glucose metabolism.

In a large occupational cohort of Korean men, baseline NAFLD was prospectively associated with incident hypertension [27]. Another study of this Korean cohort, including both men and women, also showed that NAFLD was associated with the new onset of hypertension [28]. In the other direction, one study in a group of Chinese participants and one study in a group of Japanese participants showed that baseline hypertension predicted the development of incident NAFLD [29, 30]. The two studies are summarized in Table S3. In line with these observations, the present study adds new evidence to the current literature by showing that, independent of VAT, baseline elevated blood pressure, particularly DBP, was a strong predictor of incident fatty liver and increased liver fat may also contribute to the development of incident hypertension.

A recent review article, which summarized findings from 19 prospective studies, suggested that NAFLD may be a precursor of metabolic syndrome, however, most of these studies used serum enzymes such as gamma-glutamyl transferase as a proxy for NAFLD [31]. In contrast, few studies showed that metabolic syndrome precedes the development of NAFLD [29, 32]. For example, Wong et al. showed that baseline metabolic syndrome was a predictor of incident NAFLD (Table S3) [32]. Similarly, it seems that NAFLD may develop either before or after the onset of hypertriglyceridemia, a key component of metabolic syndrome [32-34]. In the present study, we observed that metabolic syndrome and hypertriglyceridemia were predictors of incident fatty liver, but fatty liver at baseline was not associated with incident metabolic syndrome or incident hypertriglyceridemia. The discrepancy between our findings and others may be due to different liver fat measurements or different study samples. Nevertheless, more studies utilizing longitudinal data are needed to explore the bi-directional association between NAFLD and CVD risk factors. Additionally, integrating genotype data of NAFLD or CVD risk factors into future studies, e.g., Mendelian randomization analysis [35], may help to confirm the observed relationship.

It is possible that insulin resistance plays an important role linking the bi-directional association of fatty liver and CVD risk factors. Insulin resistance, the underlying cause of metabolic syndrome and its components [36], may lead to the overproduction of very low-density lipoproteins and increased influx of free fatty acids from adipose tissue into the liver, which trigger hepatic steatosis [37]. On the other hand, when hepatic steatosis is present, intermediate products in the process of lipolysis or de novo lipogenesis such as diacylglycerol may further damage insulin signaling pathways [38].

The prevalence of NAFLD is 20-30% and expected to increase in the US and worldwide [1, 2]. NAFLD is not only associated with the development of hypertension and type 2 diabetes, it causes chronic liver disease [39]. It has been projected that NAFLD will become the top indication for liver transplantation in the coming decades [40, 41]. The present study provides new evidence to show that NAFLD may play an important role in the pathogenesis of hypertension and type 2 diabetes. In addition, our findings suggest that prevention of NAFLD may need a rigorous intervention and prevention strategy to eliminate CVD risk factors.

The strengths of the present study include the prospective study design with 6 years of follow-up, the consideration of a comprehensive list of lifestyle and clinical covariates carefully assessed using standardized measurements. There are several limitations that warrant mention. MDCT may not be sensitive to mild hepatic steatosis [42], which may lead to misclassification. Additionally, the present study did not consider secondary causes for NAFLD, i.e., causes other than heavy alcohol consumption such as viral infection and drugs that may alter liver metabolism; however, the prevalence of these conditions is likely to be low in our community-based sample. Our study participants are at their middle- to older-age and the majority are white, which limit the generalizability to other, more diverse, populations.

The present study demonstrated bi-directional relationships between fatty liver and CVD risk factors over 6-year of follow-up in a group of middle-aged to older adults. Future

studies are needed to examine if interventions may reduce the burden of CVD risk factors and NAFLD, as well as to examine the pathways underlying the association of NAFLD and CVD risk factors.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Abbreviation

| | |
|---|---|
| **BMI** | body mass index |
| **CVD** | cardiovascular vascular disease |
| **DBP** | diastolic blood pressure |
| **HDLc** | high density lipoprotein cholesterol |
| **LPR** | liver-phantom ratio |
| **MDCT** | multi-detector computed tomography |
| **NAFLD** | non-alcoholic fatty liver disease |
| **SBP** | systolic blood pressure |
| **VAT** | visceral adipose tissue |

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## Lay summary

It is not fully understood whether non-alcoholic fatty liver (NAFLD) disease precedes or develops after increased cardiovascular disease (CVD) risk factors. The findings of our study suggest a bi-directional relationship between NAFLD and CVD risk factors.

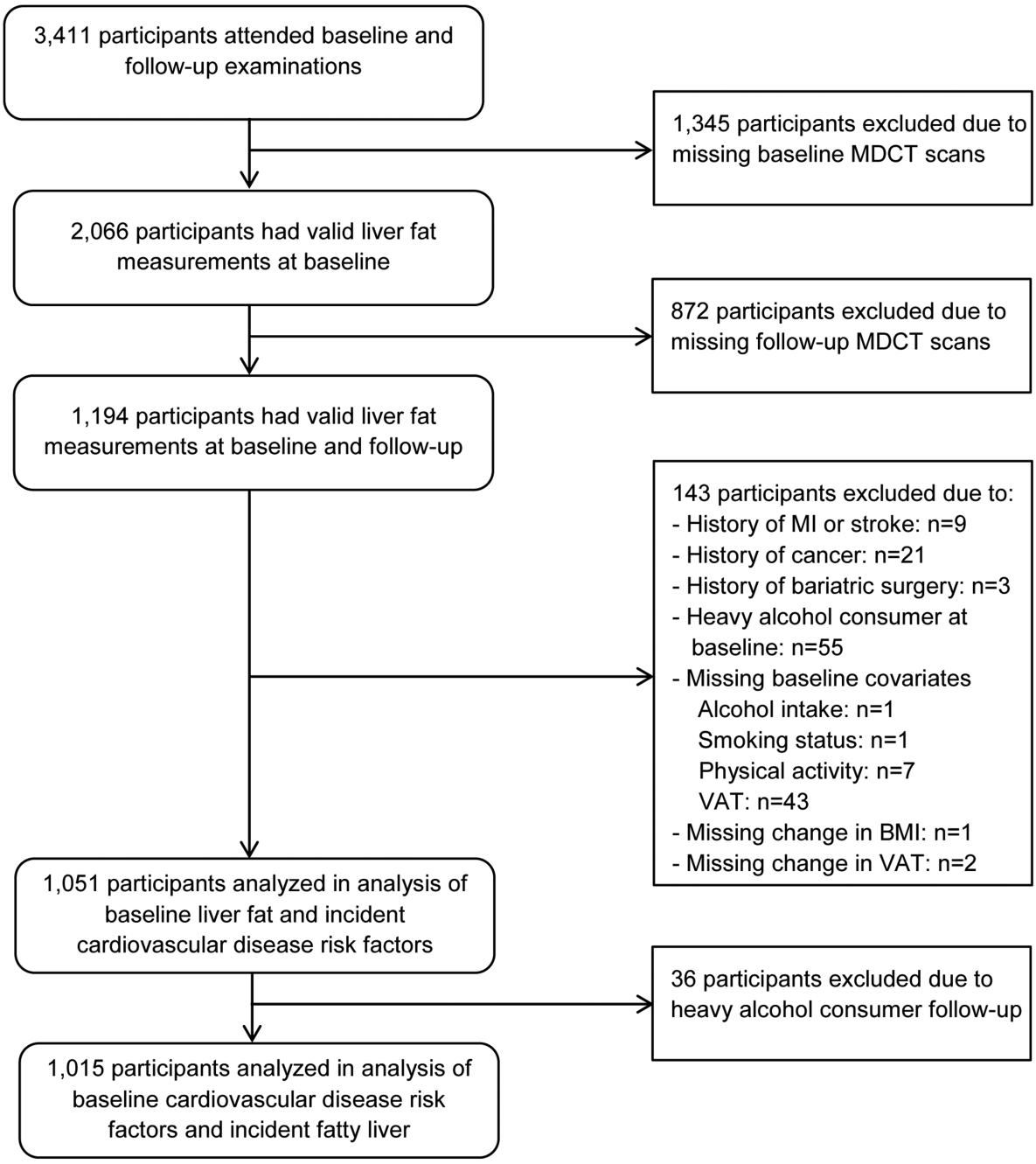


**Figure 1.**

Study sample in analyses of bidirectional relationship between fatty liver and cardiovascular disease risk factors. MDCT: multi-detector computed tomography; VAT: visceral adipose tissue.

## Table 1

Baseline characteristics of 1,051 participants with and without prevalent fatty liver[1]

| | Fatty Liver[3] | No Fatty liver | P-value[4] |
|---|---|---|---|
| N (%) | 187 (17.8) | 864 (82.2) | |
| Liver-phantom ratio | 38.5 ± 5.7 | 37.6 ± 2.2 | <0.001 |
| Age, years | 46.5 ± 6.8 | 45.0 ± 6.1 | 0.003 |
| Women, %(n) | 49 (91) | 45 (388) | 0.83 |
| Alcohol, servings/week | 4.3 ± 5.5 | 4.3 ± 4.6 | 0.35 |
| Current smoking, %(n) | 12 (22) | 9 (80) | 0.24 |
| Physical activity score | 36.1 ± 7.1 | 37.5 ± 7.9 | 0.04 |
| Body mass index, $kg/m^2$ | 30.1 ± 5.9 | 26.6 ± 4.6 | < 0.001 |
| Visceral adipose tissue ($cm^3$) | 2148 ± 1032 | 1428 ± 800 | <0.001 |
| Systolic blood pressure, mm Hg | 124.5 ± 16.6 | 117.8 ± 13.4 | <0.001 |
| Diastolic blood pressure, mm Hg | 79.1 ± 9.0 | 75.9 ± 8.9 | <0.001 |
| Hypertension meds, %(n) | 22 (41) | 9 (74) | <0.001 |
| Hypertension, %(n) | 34 (64) | 17 (145) | <0.001 |
| Triglycerides, mg/dL[2] | 137 (109) | 89 (63) | <0.001 |
| High density lipoprotein, mg/dL | 48.5 ± 16.1 | 55.1 ± 16.7 | <0.001 |
| Lipid lowering meds, %(n) | 13 (24) | 9 (81) | 0.24 |
| Hypertriglyceridemia, %(n) | 48 (90) | 25 (214) | <0.001 |
| Low high density lipoprotein, %(n) | 43 (81) | 24 (206) | <0.001 |
| Fasting plasma glucose, mg/dL | 103.9 ± 27.2 | 95.2 ± 16.5 | <0.001 |
| Hypoglycemic meds, %(n) | 6 (11) | 1 (10) | <0.001 |
| Impaired fasting glucose, %(n) | 39 (67) | 22 (189) | <0.001 |
| Type 2 diabetes, %(n) | 8 (14) | 2 (13) | <0.001 |
| Metabolic syndrome, %(n) | 53 (99) | 19 (164) | <0.001 |

[1] Mean and standard deviation or proportion (counts)

[2] Median and interquartile range

[3] Fatty liver was defined as liver-phantom ratio ≤ sex-specific 20 percentiles (32.8 in men and 34.0 in women)

[4] sex- and age-adjusted P-value

## Table 2

Prospective association between baseline liver fat and incident CVD risk factors over 6 years

| | | Continuous liver-phantom ratio (per standard deviation decrease) | | Dichotomous liver-phantom ratio (fatty liver[1] vs. no fatty liver) | |
|---|---|---|---|---|---|
| | N= | Odds ratio (95%CI) | *p* | Odds ratio (95%CI) | *p* |
| Metabolic syndrome | | | | | |
| Model | 798 | 1.15 (0.84, 1.58) | 0.38 | 1.37 (0.69, 2.72) | 0.37 |
| Model +BMI | 798 | 0.95 (0.67, 1.35) | 0.78 | 0.88 (0.41, 1.89) | 0.74 |
| Model +VAT | 798 | 0.91 (0.65, 1.29) | 0.61 | 0.89 (0.43, 1.85) | 0.76 |
| Model +BMI+ΔBMI+ΔLPR | 798 | 0.95 (0.64, 1.43) | 0.81 | 0.92 (0.40, 2.14) | 0.85 |
| Model +VAT+ΔVAT+ΔLPR | 798 | 0.91 (0.60, 1.39) | 0.67 | 0.84 (0.38, 1.89) | 0.68 |
| Hypertension | | | | | |
| Model | 840 | 1.42 (1.15, 1.76) | 0.001 | 1.79 (1.04, 3.06) | 0.03 |
| Model +BMI | 840 | 1.36 (1.10, 1.68) | 0.004 | 1.54 (0.88, 2.68) | 0.13 |
| Model +VAT | 840 | 1.28 (1.02, 1.59) | 0.03 | 1.33 (0.75, 2.36) | 0.34 |
| Model +BMI+ΔBMI+ΔLPR | 840 | 1.37 (1.09, 1.70) | 0.01 | 1.48 (0.83, 2.63) | 0.18 |
| Model +VAT+ΔVAT+ΔLPR | 840 | 1.35 (1.07, 1.71) | 0.01 | 1.34 (0.74, 2.41) | 0.33 |
| Hypertriglyceridemia | | | | | |
| Model | 813 | 0.85 (0.62, 1.17) | 0.33 | 0.65 (0.31, 1.37) | 0.26 |
| Model +BMI | 813 | 0.85 (0.62, 1.18) | 0.33 | 0.65 (0.30, 1.39) | 0.26 |
| Model +VAT | 813 | 0.81 (0.57, 1.13) | 0.21 | 0.59 (0.27, 1.28) | 0.18 |
| Model +BMI+ΔBMI+ΔLPR | 813 | 0.94 (0.66, 1.34) | 0.73 | 0.68 (0.30, 1.51) | 0.34 |
| Model +VAT+ΔVAT+ΔLPR | 813 | 0.95 (0.66, 1.36) | 0.76 | 0.70 (0.32, 1.55) | 0.38 |
| Low high-density lipoprotein | | | | | |
| Model | 763 | 0.97 (0.63, 1.48) | 0.87 | 0.97 (0.35, 2.72) | 0.95 |
| Model +BMI | 763 | 0.93 (0.60, 1.43) | 0.74 | 0.87 (0.30, 2.53) | 0.79 |
| Model +VAT | 763 | 0.96 (0.61, 1.50) | 0.85 | 0.96 (0.33, 2.81) | 0.94 |
| Model +BMI+ΔBMI+ΔLPR | 763 | 0.95 (0.62, 1.47) | 0.83 | 0.90 (0.31, 2.63) | 0.84 |
| Model +VAT+ΔVAT+ΔLPR | 763 | 1.01 (0.63, 1.61) | 0.97 | 0.97 (0.33, 2.84) | 0.95 |
| Impaired fasting glucose | | | | | |
| Model | 756 | 1.28 (1.03, 1.60) | 0.03 | 1.75 (1.03, 2.98) | 0.04 |
| Model +BMI | 756 | 1.19 (0.95, 1.48) | 0.13 | 1.35 (0.77, 2.36) | 0.30 |
| Model +VAT | 756 | 1.17 (0.93, 1.47) | 0.18 | 1.40 (0.80, 2.44) | 0.24 |
| Model +BMI+ΔBMI+ΔLPR | 756 | 1.23 (0.97, 1.57) | 0.09 | 1.37 (0.77, 2.44) | 0.29 |
| Model +VAT+ΔVAT+ΔLPR | 756 | 1.31 (1.02, 1.67) | 0.03 | 1.61 (0.91, 2.85) | 0.10 |
| Type 2 diabetes | | | | | |
| Model | 1023 | 1.43 (1.09, 1.88) | 0.01 | 2.75 (1.35, 5.61) | 0.005 |
| Model +BMI | 1023 | 1.33 (1.01, 1.76) | 0.04 | 2.38 (1.15, 4.91) | 0.02 |
| Model +VAT | 1023 | 1.35 (1.00, 1.83) | 0.05 | 2.46 (1.17, 5.15) | 0.02 |
| Model +BMI+ΔBMI+ΔLPR | 1023 | 1.53 (1.14, 2.05) | 0.005 | 2.85 (1.36, 5.97) | 0.006 |
| Model +VAT+ΔVAT+ΔLPR | 1023 | 1.44 (1.05, 1.98) | 0.02 | 2.66 (1.24, 5.74) | 0.01 |

Model was adjusted for age, sex, baseline current smoking, baseline physical activity, and baseline alcohol intake. In addition, baseline cardiovascular disease risk factors were adjusted for appropriately (i.e., baseline systolic blood pressure and diastolic blood pressure in analysis of

incident hypertension; baseline triglycerides in analysis of incident hypertriglyceridemia; baseline high-density lipoprotein in analysis of incident low high-density lipoprotein; baseline plasma glucose in analysis of incident impaired fasting glucose and incident type 2 diabetes; and all baseline cardiovascular disease risk factors in analysis of incident metabolic syndrome)

VAT: visceral adipose tissue; LPR: liver-phantom ratio

[1] Fatty liver was defined as liver-phantom ratio ≤ sex-specific 20$^{th}$ percentiles at baseline examination (32.8 in men and 34.0 in women)

## Table 3

Prospective association of baseline continuous CVD risk factors and incident fatty liver over 6 years

| | Incident fatty liver[1] | | |
|---|---|---|---|
| | N= | Odds ratio (95%CI)[2] | *p* |
| Systolic blood pressure | | | |
| Model | 770 | 1.56 (1.19, 2.04) | 0.001 |
| Model +BMI | 770 | 1.29 (0.95, 1.74) | 0.10 |
| Model +VAT | 770 | 1.31 (0.98, 1.76) | 0.07 |
| Model +BMI+ΔBMI | 770 | 1.42 (1.04, 1.94) | 0.03 |
| Model +VAT+ΔVAT | 770 | 1.35 (0.99, 1.86) | 0.06 |
| Diastolic blood pressure | | | |
| Model | 769 | 2.03 (1.53, 2.69) | <0.001 |
| Model +BMI | 769 | 1.72 (1.27, 2.33) | <0.001 |
| Model +VAT | 769 | 1.66 (1.23, 2.26) | 0.001 |
| Model +BMI+ΔBMI | 769 | 1.87 (1.37, 2.55) | <0.001 |
| Model +VAT+ΔVAT | 769 | 1.68 (1.21, 2.32) | 0.002 |
| Triglycerides (logged) | | | |
| Model | 764 | 1.81 (1.38, 2.38) | <0.001 |
| Model +BMI | 764 | 1.41 (1.05, 1.89) | 0.02 |
| Model +VAT | 764 | 1.31 (0.97, 1.77) | 0.08 |
| Model +BMI+ΔBMI | 764 | 1.54 (1.14, 2.09) | 0.005 |
| Model +VAT+ΔVAT | 764 | 1.53 (1.09, 2.13) | 0.01 |
| High-density lipoprotein | | | |
| Model | 764 | 0.79 (0.59, 1.06) | 0.12 |
| Model +BMI | 764 | 1.05 (0.77, 1.45) | 0.74 |
| Model +VAT | 764 | 1.09 (0.79, 1.51) | 0.59 |
| Model +BMI+ΔBMI | 764 | 0.93 (0.66, 1.32) | 0.69 |
| Model +VAT+ΔVAT | 764 | 0.92 (0.63, 1.33) | 0.66 |
| Fasting plasma glucose | | | |
| Model | 830 | 3.56 (2.19, 5.79) | <0.001 |
| Model +BMI | 830 | 1.94 (1.15, 3.28) | 0.01 |
| Model +VAT | 830 | 2.00 (1.17, 3.40) | 0.01 |
| Model +BMI+ΔBMI | 830 | 2.29 (1.33, 3.93) | 0.003 |
| Model +VAT+ΔVAT | 830 | 1.99 (1.14, 3.47) | 0.01 |

Model was adjusted for age, sex, baseline current smoking, baseline physical activity, baseline alcohol intake, and baseline liver fat

VAT: visceral adipose tissue

[1] Incident fatty liver was defined as liver-phantom ratio ≤ sex-specific 20$^{th}$ percentiles at follow-up examination (30.0 in men and 32.9 in women) after exclusion of participants with fatty liver at baseline

[2] Odds ratio was for per standard deviation increase of continuous CVD risk factors

## Table 4

Prospective association of baseline dichotomous CVD risk factors and incident fatty liver over 6 years

| | | Incident fatty liver[1] | |
|---|---|---|---|
| | N= | Odds ratio (95%CI) | *p* |
| Metabolic syndrome vs. No metabolic syndrome | | | |
| Model | 841 | 4.63 (2.87, 7.47) | <0.001 |
| Model +BMI | 841 | 2.03 (1.18, 3.50) | 0.01 |
| Model +VAT | 841 | 2.12 (1.22, 3.67) | 0.008 |
| Model +BMI+ΔBMI | 841 | 2.42 (1.37, 4.28) | 0.002 |
| Model +VAT+ΔVAT | 841 | 2.36 (1.29, 4.32) | 0.005 |
| Hypertension vs. No hypertension | | | |
| Model | 841 | 3.34 (2.04, 5.49) | <0.001 |
| Model +BMI | 841 | 2.34 (1.38, 3.99) | 0.002 |
| Model +VAT | 841 | 2.23 (1.30, 3.80) | 0.003 |
| Model +BMI+ΔBMI | 841 | 2.61 (1.50, 4.56) | 0.001 |
| Model +VAT+ΔVAT | 841 | 2.27 (1.27, 4.06) | 0.006 |
| Hypertriglyceridemia vs. No hypertriglyceridemia | | | |
| Model | 840 | 3.04 (1.84, 5.02) | <0.001 |
| Model +BMI | 840 | 2.02 (1.18, 3.44) | 0.01 |
| Model +VAT | 840 | 1.83 (1.08, 3.12) | 0.03 |
| Model +BMI+ΔBMI | 840 | 2.22 (1.28, 3.88) | 0.005 |
| Model +VAT+ΔVAT | 840 | 2.16 (1.21, 3.86) | 0.009 |
| Low high-density lipoprotein cholesterol vs. No low high-density lipoprotein cholesterol | | | |
| Model | 840 | 1.46 (0.91, 2.35) | 0.12 |
| Model +BMI | 840 | 0.96 (0.57, 1.62) | 0.89 |
| Model +VAT | 840 | 0.86 (0.51, 1.45) | 0.56 |
| Model +BMI+ΔBMI | 840 | 1.20 (0.70, 2.07) | 0.50 |
| Model +VAT+ΔVAT | 840 | 1.03 (0.59, 1.81) | 0.92 |
| Impaired fasting glucose vs. No impaired fasting glucose | | | |
| Model | 828 | 2.92 (1.76, 4.82) | <0.001 |
| Model +BMI | 828 | 1.78 (1.04, 3.05) | 0.04 |
| Model +VAT | 828 | 1.69 (0.98, 2.90) | 0.06 |
| Model +BMI+ΔBMI | 828 | 1.92 (1.09, 3.37) | 0.02 |
| Model +VAT+ΔVAT | 828 | 1.86 (1.04, 3.32) | 0.04 |
| Type 2 diabetes vs. No type 2 diabetes | | | |
| Model | 841 | 4.15 (1.19, 14.46) | 0.03 |
| Model +BMI | 841 | 3.67 (0.94, 14.29) | 0.06 |
| Model +VAT | 841 | 4.27 (1.08, 16.85) | 0.04 |
| Model +BMI+ΔBMI | 841 | 5.21 (1.28, 21.21) | 0.02 |
| Model +VAT+ΔVAT | 841 | 6.69 (1.64, 27.36) | 0.008 |

Model was adjusted for age, sex, baseline current smoking, baseline physical activity, baseline alcohol intake, and baseline liver fat

VAT: visceral adipose tissue

[1] Incident fatty liver was defined as liver-phantom ratio ≤ sex-specific 20$^{th}$ percentiles at follow-up examination (30.0 in men and 32.9 in women) after exclusion of participants with fatty liver at baseline