Research Article
NAFLD and Alcohol-Related Liver Diseases

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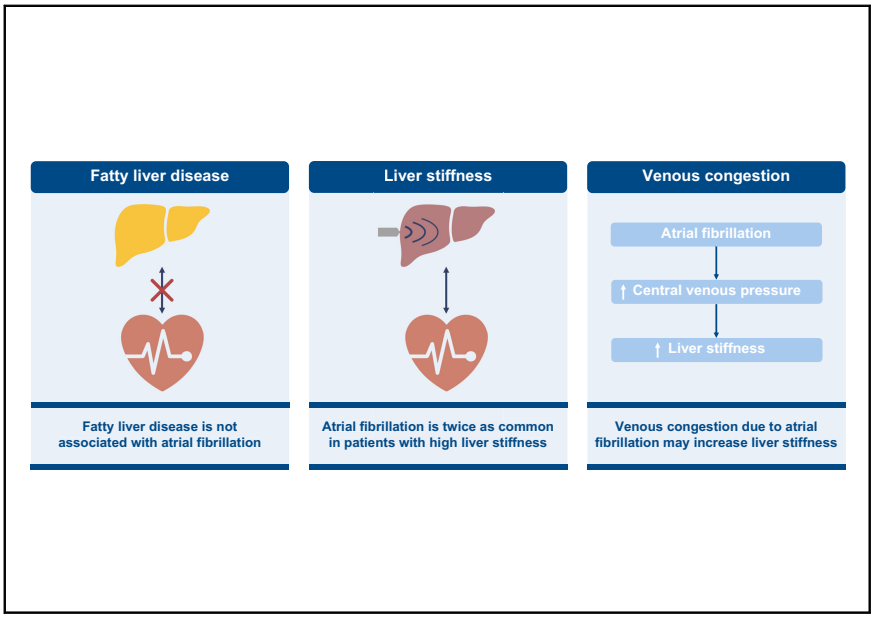
Liver stiffness not fatty liver disease is associated with atrial fibrillation: The Rotterdam study

Graphical abstract



Highlights

- Fatty liver disease is not associated with prevalent or incident atrial fibrillation.
- Liver stiffness is significantly associated with atrial fibrillation.
- Venous congestion instead of fibrosis may explain the association between liver stiffness and atrial fibrillation.
- High liver stiffness in the absence of liver disease may be due to cardiovascular disease.

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Lay summary

There have been inconsistent reports about the potential links between fatty liver disease and atrial fibrillation (an irregular and often very fast heart rhythm). Herein, we show that liver stiffness (which is a marker of liver fibrosis), but not fatty liver disease, was associated with a higher prevalence of atrial fibrillation. We hypothesis that atrial fibrillation, rather than fibrosis, may be the cause of increased liver stiffness in participants without overt liver disease.

https://doi.org/10.1016/j.jhep.2022.05.030
 J. Hepatol. 2022, 77, 931–938

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Liver stiffness not fatty liver disease is associated with atrial fibrillation: The Rotterdam study

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Background & Aims: Fatty liver disease has become the most prevalent chronic liver disease globally and is linked to cardiovascular disease, including arrhythmias. However, there have been inconsistent reports on the association between fatty liver disease and atrial fibrillation, while the role of liver stiffness in this association remains unclear.

Methods: Within the Rotterdam Study, a large prospective ongoing cohort, participants attending the abdominal ultrasound program between 2009-2014 were included. Exclusion criteria were no atrial fibrillation data or >20% missing data across analysis variables. Steatosis was assessed by ultrasound, liver stiffness by transient elastography and atrial fibrillation by 12-lead electrocardiograms. Incident atrial fibrillation was based on medical records and complete until 2014. Logistic and Cox-regression were used to quantify associations between fatty liver disease and atrial fibrillation.

Results: We included 5,825 participants (aged 69.5±9.1, 42.9% male), 35.7% had steatosis, liver stiffness measurement was available in 73.3%, and 7.0% had prevalent atrial fibrillation. Steatosis was not associated with prevalent atrial fibrillation in fully adjusted models (odds ratio [OR] 0.80; 95% CI 0.62-1.03), findings were consistent for non-alcoholic or metabolic dysfunction-associated fatty liver disease. Liver stiffness was significantly associated with prevalent atrial fibrillation (OR 1.09 per kPa, 95% CI 1.03-1.16); however, this was only persistent among those without steatosis (OR 1.18 per kPa, 95% CI 1.08-1.29). Lastly, no associations were found between steatosis (hazard ratio 0.88; 95% CI 0.59-1.33; follow-up 2.1 [1.1–3.2] years) and incident atrial fibrillation.

Conclusions: Fatty liver disease was not associated with prevalent or incident atrial fibrillation, while liver stiffness was significantly associated with atrial fibrillation, especially among those without steatosis. This association might be driven by venous congestion instead of fibrogenesis, but this awaits further validation. We recommend assessing cardiovascular health in participants with high liver stiffness, especially in the absence of overt liver disease.

Clinical trial number: NTR6831.

Lay summary: There have been inconsistent reports about the potential links between fatty liver disease and atrial fibrillation (an irregular and often very fast heart rhythm). Herein, we show that liver stiffness (which is a marker of liver fibrosis), but not fatty liver disease, was associated with a higher prevalence of atrial fibrillation. We hypothesis that atrial fibrillation, rather than fibrosis, may be the cause of increased liver stiffness in participants without overt liver disease.

Introduction

Fatty liver disease has become the most common chronic liver disease, affecting over 25% of adults globally.[1] It ranges from simple hepatic steatosis to clinically relevant fibrosis and cirrhosis, which are significant drivers for advanced liver disease and hepatocellular carcinoma.[2] However, the disease burden of fatty liver disease is not limited to hepatic complications but extends to renal dysfunction, extrahepatic malignancies and cardiovascular morbidity.[3–7]

Atrial fibrillation is a highly prevalent heart rhythm disorder that has been suggested to be associated with fatty liver disease.[8] Several mechanisms driving this association are proposed, including systemic inflammation, dyslipidemia, increased insulin resistance, and renin-angiotensin system activation.[9–11] Moreover, liver stiffness, a transient elastography-based marker for liver fibrosis, may be an important parameter in this assumed association. However, the mechanism remains unclear and results have not yet been validated.[12]

Few studies have investigated the association between fatty liver disease and atrial fibrillation, and results have been inconsistent.[13–17] These studies were hampered by biomarker-based assessment of fatty liver disease (instead of imaging), limited sample size, or failure to adjust for important confounders. Moreover, most of the studies have not assessed the role liver stiffness in the association with atrial fibrillation.

Within the large prospective population-based Rotterdam Study, we investigate the association of fatty liver disease and liver stiffness with prevalent and incident atrial fibrillation. A

Keywords: Liver stiffness; atrial fibrillation; coronary heart disease; NAFLD; MAFLD; steatosis.
Received 10 December 2021; received in revised form 5 April 2022; accepted 22 May 2022; available online 7 June 2022
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https://doi.org/10.1016/j.jhep.2022.05.030

defining feature of our study is the use of several fatty liver disease definitions and the availability of liver stiffness measurement, which altogether allows for a thorough assessment of liver health.

Patients and methods

Participants

This analysis was embedded within the Rotterdam Study, a large prospective population-based cohort study that commenced in 1989. Citizens of Ommoord, a district of Rotterdam, were selected based on zip code and were eligible to participate when at least 40 years old. Participants are invited to the Rotterdam Study research center every 4 to 6 years. Since 2009, abdominal ultrasound and transient elastography have been part of the repeated assessments within the Rotterdam Study. The study design, principles, and recent findings of the Rotterdam study were published recently.[18]

We included participants that had visited the research center between March 2009 and June 2014 and had undergone abdominal ultrasound. Participants with no data on atrial fibrillation or >20% missing data for the included variables were excluded.

Hepatology assessments

Abdominal ultrasound was performed by a single sonographer (PvW) on a Hitachi Hi-Vision 900. Measurements included craniocaudal length of the spleen and hepatic vein diameter (measured 20 mm distal of the inferior vena cava [IVC]) and the assessment of steatosis, which was based on hyperechoic liver parenchyma compared to the kidney or spleen.[19] According to the European Association for the Study of the Liver (EASL) guidelines,[20] non-alcoholic fatty liver disease (NAFLD) was defined as hepatic steatosis in the absence of secondary causes of steatosis comprising viral hepatitis (B or C), steatogenic drug use, or excessive alcohol consumption defined as ≥30 g/day for males and ≥20 g/day for females. In addition, NAFLD was excluded if quantitative alcohol data was missing in patients reporting an alcohol consumption frequency of ≥4 days a week, since we could not rule out excessive alcohol intake. Metabolic dysfunction-associated fatty liver disease (MAFLD) was defined according to the novel criteria as steatosis together with overweight/obesity, diabetes or the presence of 2 minor metabolic dysfunction criteria.[21] Liver stiffness was measured with transient elastography (FibroScan, EchoSens, Paris, France) using the same device throughout the study period. At least 10 individual measurements were required for a valid measurement with an interquartile range of ≤30% if liver stiffness exceeded 7.0 kPa.[22] High liver stiffness was defined as a valid liver stiffness measurement ≥8.0 kPa, based on prior research in the general population.[23]

Cardiovascular assessments

The 2020 ESC guidelines defined atrial fibrillation as abnormal electrocardiographic characteristics comprising irregular R-R intervals, absence of distinct repeating P waves and irregular atrial activations assessed on either a 30 second tracing electrocardiogram (ECG) or an entire 12-lead ECG.[24] In line with these guidelines, atrial fibrillation was checked for using a 10-second, entire 12-lead ECG (Esaote, Biomedical, Florence, Italy) obtained on regular visits and assessed by the Modular ECG analysis system. Two research physicians validated the automatic diagnosis of atrial fibrillation. In addition to the information from the regular study visits, data were obtained from treating physicians and used to assess prevalent and incident atrial fibrillation. These diagnoses were confirmed by independent reading of the ECG by research physicians.[25] Follow-up was complete until January 1st, 2014. Prevalent coronary heart disease (CHD) and heart failure (HF) were based on data obtained during study visits and from treating physicians. The definitions and procedures to obtain cardiovascular data in the Rotterdam Study have been described in detail previously.[25] IVC diameter was measured with an ACUSON Cypress 3V2c transducer during cardiac echocardiography.

Additional covariates

Research assistants and trained interviewers acquired data on participants' anthropometrics, alcohol consumption, smoking habits, and education level. Alcohol consumption was additionally derived from the self-completed food frequency questionnaire. Medication data were obtained from linkage with the participants' pharmacies.

Blood samples were collected while participants were fasting. Glucose, blood lipids, aspartate aminotransferase, and alanine aminotransferase were assessed by automatic enzyme procedures and insulin with automatic immunoassay (Roche, Diagnostic GmbH, Mannheim, Germany).

Diabetes was defined as fasting glucose ≥7.0 mmol/L, drug treatment for diabetes, or obtained from treating physicians' data. The metabolic syndrome was defined, in accordance with the ATP-III criteria,[26] as at least 3 of the following components: i) fasting glucose >5.6 mmol/L or anti-diabetic drug use, ii) waist circumference >102 cm for males and >88 cm for females; iii) triglycerides ≥1.7 mmol/L or statin use, iv) HDL-C <1.04 mmol/L in males and <1.30 in females or statin use and v) hypertension based on either a systolic blood pressure ≥130, diastolic blood pressure ≥85 or antihypertensive drug use.

Statistical analysis

We imputed missing values of covariates included in the main models or additional analyses to reduce potential bias from missing data. This was performed with the R-package MICE 3.13.0 under the fully conditioned specification. We created 50 imputed datasets and analyses were performed in each dataset and consequently pooled using Rubin's rules to take into account the uncertainty of the imputed values. More information regarding the imputation procedure is available in Table S1.

Participants' characteristics before imputation were described as n and %, mean and SD, or median and IQR, according to the nature of the data. In addition, imputed data was compared to non-imputed data in Table S2.

Logistic and linear regression were used to assess the associations between fatty liver disease and liver stiffness (continuous and ≥8.0 kPa) with prevalent atrial fibrillation. We used steatosis for our main analysis and results were verified by using NAFLD and MAFLD in additional analyses. We used 3 multivariable models, based on established risk factors for NAFLD and/or atrial fibrillation. Model 1 was only adjusted for age and sex. Model 2 was additionally adjusted for alcohol consumption, smoking, education level, prevalent HF, prevalent CHD, and the individual categorical components of the metabolic syndrome (high waist circumference, hypertension, hypo-HDL, hypertriglyceridemia and (pre)diabetes). Model 3 included covariates

that could affect liver stiffness by other means than fibrosis (craniocaudal spleen length, IVC diameter, liver vein diameter, and alanine aminotransferase levels)[27–29] and was therefore only applied for the analysis assessing liver stiffness. Analyses were performed among the entire population and subsequently stratified for steatosis status. Moreover, in sensitivity analyses, participants with prevalent HF and/or CHD were excluded.

Next, in longitudinal analysis, Cox proportional hazards analysis was used to assess the impact of baseline fatty liver disease (MAFLD, NAFLD and steatosis) on the risk of incident atrial fibrillation. Baseline was set on the date of abdominal ultrasound, and in addition to the general exclusion criteria, we excluded participants with prevalent atrial fibrillation or lack of follow-up for atrial fibrillation. In line with the cross-sectional analysis, results were adjusted for the covariates included in model 1 and model 2.

Last, to get further insight into which parameters might influence liver stiffness, associations with liver stiffness as an outcome and prevalent atrial fibrillation, heart failure, IVC diameter, and liver vein diameter as exposures were explored with linear regression. These analyses were performed on the non-imputed data, as in particular IVC and liver vein diameter were frequently imputed. Results were adjusted for age, sex, alcohol consumption, smoking, education, high waist circumference, hypertension, hypo-HDL, hypertriglyceridemia, and (pre)diabetes. Similarly, the associations between prevalent atrial fibrillation with IVC and liver vein diameter as well as liver stiffness have been quantified using linear regression with the same model.

All analyses were performed in R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). *P* values of <0.05 were considered statistically significant.

Results

In this cohort study, 5,967 participants underwent abdominal ultrasound, of whom 22 participants were excluded for no atrial fibrillation data and 120 participants for missing data across >20% of variables of interest, resulting in 5,825 participants for analysis (Fig. 1). The mean age was 69.5 (SD 9.1) years, 42.9% (n = 2,499) were male and mean BMI was 27.5 kg/m^2 (SD 4.3). At baseline, steatosis was present in 35.7% (n = 2,079) and atrial fibrillation in 7.0% (n = 405). Among included participants, 73.3% (n = 4,270) had a valid liver stiffness measurement and 6.1% (n = 262) had liver stiffness ≥8.0 kPa. Additional characteristics are provided in Table 1 and characteristics after imputation are provided in Table S2. A direct comparison of participants with prevalent atrial fibrillation to those without is available in Table S3.

Not fatty liver disease, but liver stiffness was associated with atrial fibrillation

Hepatic steatosis was not associated with a higher prevalence of atrial fibrillation across all multivariable models (steatosis: odds ratio [OR]model2 0.80; 95% CI 0.62–1.03, Table 2) and similar results were obtained when steatosis was replaced by NAFLD or MAFLD. In a subset without prevalent CHD and/or HF, fatty liver disease was consistently not associated with higher prevalence of atrial fibrillation (Table S4). On the other hand, liver stiffness ≥8.0 kPa was significantly associated with atrial fibrillation in fully adjusted models that included covariates affecting liver stiffness (ORmodel$_3$ 2.08; 95% CI 1.33–3.25, Table 3).

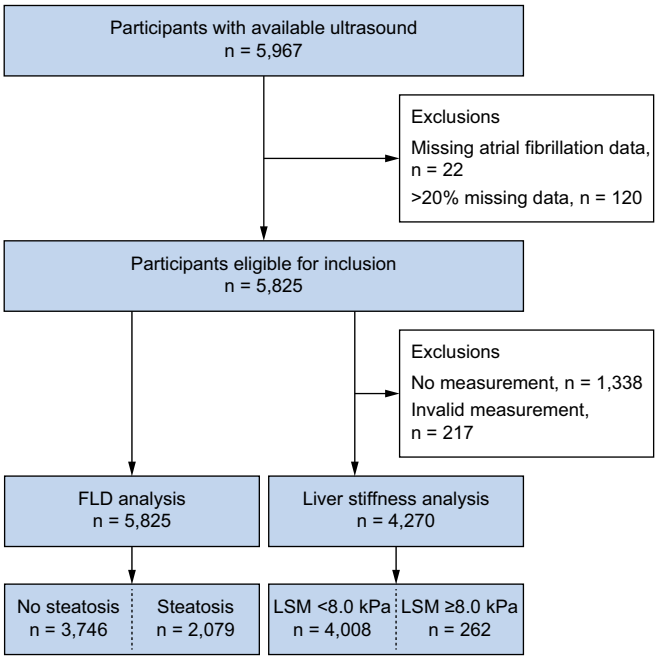

Fig. 1. Participant selection. FLD, fatty liver disease; LSM, liver stiffness measurement.

Furthermore, a similar association was observed for liver stiffness (continuous) in multivariable analysis (ORmodel$_3$ 1.09 per kPa; 95% CI 1.03–1.16, Table 3). These results were consistent in a subset of participants without prevalent CHD and/or HF (Table S5).

Liver stiffness was only associated with atrial fibrillation among those without steatosis

Associations between liver stiffness and prevalent atrial fibrillation were further examined in participants with steatosis (n = 1,440) and without steatosis (n = 2,830). For liver stiffness ≥8.0 kPa among the steatosis population, results were only significant in the age and sex-adjusted model (ORmodel$_1$ 2.22; 95% CI 1.24–4.00) and no longer after including all confounders (ORmodel$_3$ 1.68; 95% CI 0.82–3.47). This was in contrast to those without steatosis, for whom the association was statistically significant in all models (ORmodel$_3$ 2.86; 95% CI 1.56–5.22; Table 4). Similarly, liver stiffness (continuous) was not associated with atrial fibrillation in multivariable analyses in the steatosis population (ORmodel$_3$ 1.03 per kPa; 95% CI 0.95–1.11), while we observed a significant association in the no steatosis population in all models (ORmodel$_3$ 1.18 per kPa; 95% CI 1.08–1.29, Table 4).

Fatty liver disease was not associated with incident atrial fibrillation

For the longitudinal analysis, we excluded 405 participants with prevalent atrial fibrillation and 356 participants without follow-up. During a median follow-up of 2.1 [1.1-3.2] years, 132 out of 5,064 individuals had incident atrial fibrillation (incidence rate 10.2 per 1,000 person-years). Hepatic steatosis was not associated with incident atrial fibrillation (ORmodel$_2$ 0.88; 95% CI 0.59–1.38) and similar results were obtained when steatosis was replaced by NAFLD or MAFLD (Table 5).

Table 1. Participants' characteristics.

Variable	All N = 5,825	Steatosis n = 2,079	No steatosis n = 3,746
Demographics			
Age (years)	69.5 (9.1)	69.4 (8.4)	69.6 (9.4)
Male	2,499 (42.9)	942 (45.3)	1,557 (41.6)
European ancestry	5,036 (97.4)	1,813 (98.0)	3,223 (97.1)
Education			
Low	2,776 (48.2)	1,067 (52.0)	1,709 (46.0)
Intermediate	1,731 (30.0)	608 (29.7)	1,123 (30.3)
High	1,255 (21.8)	375 (18.3)	880 (23.7)
Current/former smoking	3,936 (67.7)	1,486 (71.7)	2,450 (65.5)
Alcohol intake (gram/day)	7.3 (8.2)	8.2 (9.5)	6.8 (7.3)
Physical examination			
High waist circumference*	2,584 (44.4)	1,455 (70.0)	1,129 (30.1)
BMI (kg/m^2)	27.5 (4.3)	29.9 (4.3)	26.2 (3.7)
Comorbidities			
Hypertension	4,654 (80.0)	1,798 (86.7)	2,856 (76.3)
Diabetes	873 (15.2)	493 (24.1)	380 (10.3)
Metabolic syndrome	2,897 (49.8)	1,476 (71.2)	1,421 (38.0)
Atrial fibrillation	405 (7.0)	135 (6.5)	270 (7.2)
Coronary heart disease	520 (8.9)	197 (9.5)	323 (8.6)
Heart failure	206 (3.5)	73 (3.5)	133 (3.6)
Biochemistry			
AST (U/L)	24 [21, 28]	25 [21, 29]	24 [21, 28]
ALT (U/L)	19 [15, 24]	22 [17, 28]	17 [14, 22]
HDL-C (mmol/L)	1.5 (0.4)	1.4 (0.4)	1.6 (0.4)
Triglycerides (mmol/L)	1.3 [1.0, 1.7]	1.6 [1.2, 2.1]	1.2 [0.9, 1.5]
Transient elastography			
Liver stiffness (kPa)	4.8 [3.9, 5.9]	5.1 [4.1, 6.4]	4.7 [3.8, 5.7]
Liver stiffness ≥8.0 kPa	262 (6.1)	155 (10.8)	107 (3.8)
Ultrasound			
Liver vein diameter (mm)	5.0 (1.4)	5.1 (1.4)	5.0 (1.4)
IVC diameter (mm)	17.9 (3.4)	17.6 (3.1)	18.0 (3.5)
Spleen length (cm)	9.7 (1.3)	10.0 (1.4)	9.6 (1.3)

Data is presented as mean (SD), median [IQR] or n (%).
AST, aspartate aminotransferase; ALT, alanine aminotransferase; IVC, inferior vena cava.
*Waist circumference >102 cm for male and >88 cm for female.

Liver stiffness is associated with IVC and liver vein diameter

Last we investigated the association between liver stiffness and parameters that could reflect or affect venous congestion. We observed higher liver stiffness among participants with heart failure (beta 1.75 kPa, 95% CI 1.34–2.16), which was consistent among those with and without steatosis. Similarly, among participants with steatosis, higher liver stiffness was seen for larger IVC diameter (beta 0.19 kPa per 5 mm, 95% CI 0.10–0.29) and liver vein diameter (beta 0.67 per 5 mm, 95% CI 0.42–0.91, Table 6). However, this attenuated in the steatosis population and was no longer significant. Finally, atrial fibrillation was associated with an increased IVC (+1.9 mm, 95% CI 1.56–2.28) and liver vein diameter (+0.5 mm, 95% CI 0.33–0.63) as well as increased liver stiffness (+1.1 kPa 95% CI 0.83–1.39).

Table 2. Association of fatty liver disease with prevalent atrial fibrillation.

	OR	95% CI	*p* value
Steatosis			
Model 1	0.94	0.76-1.17	0.582
Model 2	0.80	0.62-1.03	0.082
NAFLD			
Model 1	0.85	0.65-1.10	0.205
Model 2	0.76	0.57-1.02	0.071
MAFLD			
Model 1	0.96	0.77-1.20	0.735
Model 2	0.81	0.62-1.04	0.097

Results were obtained with logistic regression and given as OR with 95% CI for prevalent atrial fibrillation as outcome. Atrial fibrillation was present in 405/5,829 participants. Model 1 was adjusted for age and sex; model 2 in addition for alcohol consumption, smoking, education, high waist circumference, hypertension, hypo-HDL, hypertriglyceridemia, (pre)diabetes, coronary heart disease and heart failure.
NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.

Discussion

In this large population-based cohort study, fatty liver disease was not a risk factor for prevalent or incident atrial fibrillation. Liver stiffness, however, was associated with prevalent atrial fibrillation, which was only significant among those without steatosis. This observation might be explained by hepatic congestion driven by (subclinical) venous congestion.

Current evidence regarding the association between fatty liver disease and atrial fibrillation is inconsistent.[13–17,30,31] Interestingly, in their meta-analysis, Cai *et al.* investigated the effect of adjusting for cardiovascular risk factors and demonstrated weaker associations between fatty liver disease and atrial fibrillation after adjusting for cardiovascular risk factors (relative risk 1.19 *vs.* 1.65).[30] Moreover, they demonstrated larger effect sizes in patient cohorts with typically more metabolic comorbidity, smaller studies, and when fatty liver disease was diagnosed by fatty liver index instead of imaging. These observed differences underscore the need for a well-defined cohort with

Table 3. Association of liver stiffness with prevalent atrial fibrillation.

	OR	95% CI	*p* value
Liver stiffness ≥8.0 kPa			
Model 1	2.82	1.91-4.15	<0.001
Model 2	2.49	1.63-3.79	<0.001
Model 3	2.08	1.33-3.25	0.001
Liver stiffness (kPa)			
Model 1	1.15	1.10-1.21	<0.001
Model 2	1.12	1.07-1.18	<0.001
Model 3	1.09	1.03-1.16	0.002

Results were obtained with logistic regression and given as OR with 95% CI for prevalent atrial fibrillation as outcome. Atrial fibrillation was present in 209/4270 participants.
Model 1 was adjusted for age and sex; model 2 in addition for alcohol consumption, smoking, education, high waist circumference, hypertension, hypo-HDL, hypertriglyceridemia, (pre)diabetes, coronary heart disease and heart failure; model 3 in addition for spleen size, inferior vena cava diameter, liver vein diameter and alanine aminotransferase.
OR, odds ratio.

an accurate steatosis assessment and accurate adjustment for relevant confounders.

In our large general population-based study, we did not identify abdominal ultrasound-based fatty liver disease as an independent risk factor for prevalent or incident atrial fibrillation among the elderly. Compared to other studies, our population is older, has more age-related comorbidity, such as diabetes and hypertension, but has one of the lowest average BMIs reported in studies assessing NAFLD and atrial fibrillation. Trends between NAFLD and atrial fibrillation were more clear in studies among morbid populations (*e.g.* high BMI), which may have contributed to not demonstrating an association with NAFLD and atrial fibrillation in our study.[11,30] Nonetheless, this confirms that in the general population, the role of fatty liver disease in the development of atrial fibrillation is limited as suggested previously[30] or might not exist at all, especially after adjusting for confounders such as hypertension, dyslipidemia, (pre)diabetes, waist circumference and prevalent heart diseases.

Fatty liver disease is undisputedly associated with fibrogenesis as reflected by higher liver stiffness. A few studies have already investigated the association of fibrosis or liver stiffness with atrial fibrillation. For example, an association was demonstrated between atrial fibrillation and liver stiffness in a rather small study (n = 76) among the Finnish elderly.[12] In addition, fibrosis-4 (FIB-4) and APRI (aspartate aminotransferase-to-platelet ratio index), markers for fibrosis, were associated with atrial fibrillation among patients with NAFLD.[32] However, using biomarker-based algorithms to assess fibrosis limits the possibility for accurate adjustment, given that those algorithms themselves include relevant predictors for atrial fibrillation (*e.g.* FIB-4 includes age).

Our study assessed liver stiffness in the entire cohort by transient elastography and demonstrated that liver stiffness was associated with prevalent atrial fibrillation. Interestingly, the association between liver stiffness and prevalent atrial fibrillation turned out to be substantially higher and only significant among those without steatosis. This indicates that fatty liver disease is unlikely to be the driver for higher liver stiffness among individuals with atrial fibrillation. Furthermore, it is up for debate whether higher liver stiffness was caused by fibrogenesis, since the association was only demonstrated among those without steatosis (and thus at lowest risk for fibrosis). We note, however, that individuals without steatosis but with high liver stiffness might have “burnout NAFLD”. However, among individuals that underwent a CT scan 4-5 years prior to liver stiffness measurement, there was only evidence for hepatic steatosis in 1/35 patients with fibrosis but no steatosis at the current visit. “Burnout NAFLD” is therefore unlikely to explain the association between liver stiffness and atrial fibrillation among those without steatosis.

Liver stiffness is not a direct measurement for fibrosis, but a derivative that could also be affected by portosystemic congestion, inflammation, cholestasis and central venous pressure.[27–29] The latter is of particular interest since individuals with atrial fibrillation have higher right atrium pressure,[33] which is associated with (subclinical) venous congestion in the liver.[34] Similarly, we demonstrated larger IVC and liver vein diameter among those with prevalent atrial fibrillation, indicating (subclinical) venous congestion. Our results support that subtle signs of congestion might be associated with increased liver stiffness, since not only heart failure but also increased IVC or hepatic vein diameter were associated with higher liver stiffness. This suggests that the association between liver stiffness and atrial fibrillation could be explained by venous congestion, implicating reverse causality by (cardiovascular conditions causing) atrial fibrillation. Interestingly, results were consistent after excluding participants with CHD and HF, supporting an independent role for atrial fibrillation, via venous congestion, in the development of liver stiffness.

Venous congestion might eventually result in fibrosis since prolonged exposure to hepatic congestion can lead to hepatocyte

Table 4. Association of fibrosis and liver stiffness with prevalent atrial fibrillation stratified for steatosis.

	Steatosis			No steatosis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Liver stiffness ≥ 8.0 kPa						
Model 1	2.22	1.24-4.00	0.008	3.62	2.12-6.19	<0.001
Model 2	1.87	0.95-3.69	0.070	3.55	2.01-6.25	<0.001
Model 3	1.68	0.82-3.47	0.157	2.86	1.56-5.22	0.001
Liver stiffness (kPa)						
Model 1	1.10	1.03-1.17	0.003	1.25	1.15-1.36	<0.001
Model 2	1.05	0.98-1.13	0.196	1.23	1.12-1.34	<0.001
Model 3	1.03	0.95-1.11	0.475	1.18	1.08-1.29	<0.001

Results were obtained with logistic regression and given as OR with 95% CI for prevalent atrial fibrillation as outcome. 70/1,440 participants with steatosis had atrial fibrillation and 139/2,830 of those without steatosis. Model 1 was adjusted for age and sex; model 2 in addition for alcohol consumption, smoking, education, high waist circumference, hypertension, hypo-HDL, hypertriglyceridemia, (pre)diabetes, coronary heart disease and heart failure; model 3 in addition for spleen size, inferior vena cava diameter, liver vein diameter and alanine aminotransferase.

Table 5. Association of fatty liver disease and liver stiffness with incident atrial fibrillation.

	HR	95% CI	*p* value
Steatosis			
Model 1	0.95	0.66-1.37	0.793
Model 2	0.88	0.59-1.33	0.548
NAFLD			
Model 1	0.88	0.57-1.35	0.544
Model 2	0.86	0.53-1.38	0.522
MAFLD			
Model 1	0.98	0.68-1.42	0.912
Model 2	0.91	0.60-1.38	0.657

Results were obtained with Cox regression and given as HR with 95% CI for incident atrial fibrillation as outcome. Incident atrial fibrillation occurred in 132/5,064 participants. Model 1 was adjusted for age and sex; model 2 in addition for alcohol consumption, smoking, education, high waist circumference, hypertension, hypo-HDL, hypertriglyceridemia, (pre)diabetes, coronary heart disease and heart failure.
HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease.

atrophy via increased sinusoidal pressure, known as congestive hepatopathy.[35] Within our data, the association between atrial fibrillation and liver stiffness attenuated (but remained significant), after additional adjustment for covariates reflecting venous congestion. This supports that the association between atrial fibrillation and liver stiffness is partially (but not fully) explained by venous congestion and allows for a role of (advanced) fibrosis. However, IVC and liver veins are imperfect markers for subclinical venous congestion, and residual confounding should thus be considered. Therefore, further research, preferably with histological evidence in addition to liver stiffness measurements and objective measurements of systemic venous pressure, is warranted.

If the association between NAFLD and atrial fibrillation is predominantly driven by venous congestion, currently used cut-offs for liver fibrosis (*e.g.* ≥8.0 kPa) may need to be reassessed in patients with atrial fibrillation and other cardiovascular diseases that could result in venous congestion. Moreover, individuals with high liver stiffness in the absence of overt liver disease might benefit from cardiovascular assessment, given the apparent capability of cardiovascular disease to increase liver stiffness. These findings are especially relevant now that transient elastography is regularly applied among those without liver disease. For example, the novel EASL guideline on non-invasive tests recommends transient elastography to screen for advanced liver disease among those with metabolic dysfunction and intermediate-to-high FIB-4, which is highly common among the elderly.[36,37] As the prevalence of cardiovascular disease increases by age, the specificity of liver stiffness to detect fibrosis will attenuate. Future studies should assess whether this, in specific subgroups, eventually leads to detecting more cardiovascular disease than liver disease and thus initial (or simultaneous) referral to a cardiologist seems indicated. Furthermore, our results suggest that future studies using liver stiffness as an outcome should consider addressing the impact of cardiovascular disease on their results.

Table 6. Association of heart failure, IVC and liver vein diameter with liver stiffness.

	β	95% CI	*p* value
All participants			
Heart failure	1.75	1.34–2.16	<0.001
IVC ø (per 5 mm)	0.13	0.04–0.23	0.005
Liver vein ø (per 5 mm)	0.58	0.35–0.81	<0.001
Steatosis			
Heart failure	2.95	2.10–3.79	<0.001
IVC ø (per 5 mm)	-0.03	-0.25 to 0.20	0.816
Liver vein ø (per 5 mm)	0.35	-0.17 to 0.87	0.188
No steatosis			
Heart failure	1.09	0.66–1.52	<0.001
IVC ø (per 5 mm)	0.19	0.10–0.29	<0.001
Liver vein ø (per 5 mm)	0.67	0.42–0.91	<0.001

Results were obtained with linear regression and given as beta with 95% CIs with liver stiffness as outcome. Results were adjusted for age, sex, alcohol consumption, smoking, education, high waist circumference, hypertension, hypo-HDL, hypertriglyceridemia and (pre)diabetes.
IVC, inferior vena cava.

Although this is one of the most extensive studies investigating prevalent and incident atrial fibrillation with steatosis assessment by ultrasound and liver stiffness data, the following limitations need to be mentioned. First, our study population has a mean age of 69.5 years and is almost entirely of European ancestry (97.4%). While atrial fibrillation is increasingly prevalent at this age, the generalizability of our results might be limited, especially to younger and multi-ethnic populations. Second, the results derived from the cross-sectional analysis could not be used to study causality. Moreover, in the subgroup analysis assessing the association between liver stiffness and atrial fibrillation among individuals with steatosis, only 70 individuals had atrial fibrillation. Therefore, the final models in certain subgroups could have been overfitted and should be interpreted with caution. However, we used all 3 models throughout our cross-sectional analysis regarding liver stiffness to allow for a fair comparison between different subgroups. Third, our longitudinal analysis was hampered by a short follow-up duration and cases may have been missed since atrial fibrillation is often subclinical or paroxysmal. Fourth, the gold standard to assess steatosis and fibrosis is liver biopsy. However, since a biopsy is invasive and prone to severe complications, exposing a healthy cohort to these risks is unethical. Therefore, we used abdominal ultrasound and transient elastography to assess steatosis and fibrosis, which correlate strongly with histological findings.[38] However, we note that ultrasound has limited sensitivity in detecting mild steatosis.[20]

In conclusion, fatty liver disease was not associated with prevalent or incident atrial fibrillation in our large population-based study. In contrast, higher liver stiffness, in particular among those without steatosis, was associated with prevalent atrial fibrillation. Awaiting validation, our results indicate that this association could be driven by venous congestion instead of fibrogenesis. Since this study indicates that increased liver stiffness may result from conditions originally not linked with liver disease, further research is required to determine if the same liver stiffness cut-offs for fibrosis are applicable in participants with concomitant atrial fibrillation. For now, we recommend assessing cardiovascular health in participants with high liver stiffness, especially in the absence of overt liver disease.

Abbreviations

CHD, coronary heart disease; EASL, European Association for the Study of the Liver; ECG, electrocardiogram; FIB-4, fibrosis-4; HF, heart failure; IVC, inferior vena cava; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease.

Financial support

The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research institute for Diseases in the Elderly (Ride), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII) and the Municipality of Rotterdam. Financial support was also provided by the Foundation for Liver and Gastrointestinal Research, Rotterdam, the Netherlands. This study is further supported by the Gender and Prevention grant (555003017) from ZonMw. Zuolin Lu is a recipient of a scholarship under the China Scholarship Council (CSC) (201906940022). The funding sources were not involved in study design, data collection, analysis and interpretation of the data, nor the writing of the report and decision to submit for publication.

Conflicts of interest

RdK is a consultant and speaker for AbbVie, BMS, Gilead, Janssen, Merck, Norgine and received grants from Abbvie, Gilead, Janssen and BMS. The remaining authors reported no relevant conflicts.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study design: LvK, RdK; Data analysis and writing of the manuscript: LvK, ZL, RdK, MK

Critical review of the manuscript and approval of final version: LvK, ZL, NdG, AI, MK, RdK

All authors approve the submission of the manuscript.

Data availability statement

Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

Ethics

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Acknowledgements

We gratefully acknowledge the contribution of the participants of the Rotterdam Study, research assistants (particularly Paulien van Wijngaarden for performing the liver ultrasounds), the general practitioners, hospitals, and pharmacies in Rotterdam.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.05.030.

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Author names in bold designate shared co-first authorship

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