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Fatty liver disease is not associated with increased mortality in the elderly: A prospective cohort study

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Abstract

Background and Aims: Fatty liver disease (FLD) has been associated with excess mortality. Screening for hepatic steatosis (HS) in patients with metabolic dysfunction is therefore recommended by several guidelines, despite a paucity of evidence on the clinical relevance of FLD in this specific subgroup.

Approach and Results: We studied participants of an ongoing prospective cohort (the Rotterdam Study). Persons ≥ 65 years old were enrolled from 2009 to 2014 and were followed through 2018. Steatosis was assessed by ultrasound and liver stiffness (LS) by transient elastography. The association between HS and LS with mortality was assessed using Cox regression analysis adjusted for age, sex, education, smoking, individual components of metabolic syndrome (MetS), heart failure, coronary heart disease, and stroke. We included 4093 elderly participants (74.4 ± 6.6 years old; 42.7% male); 36.8% had ultrasound-based steatosis. During the median follow-up of 6.9 years, 793 participants died (29.6 per 1000 person-years). In the overall population, steatosis was not associated with mortality in multivariable analysis (adjusted HR [aHR], 0.87; 95% CI, 0.73–1.03). Findings were consistent across a range of clinically relevant subgroups, including age categories, sex, MetS, elevated liver enzymes, and cardiac disease. Sensitivity analyses showed similar results for mortality beyond 5 years of follow-up and cancer-related and cerebro-cardiovascular mortality. Furthermore, among participants with steatosis, higher LS (aHR, 1.04 per kPa; 95% CI, 0.95–1.14) was not associated with mortality.

Conclusions: Presence of FLD was not associated with mortality in this

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cohort nor in a range of subgroups. This indicates that screening for FLD and/or fibrosis is unlikely to improve outcomes among the elderly population.

INTRODUCTION

Fatty liver disease (FLD) has become the most common cause of chronic liver disease in many Western countries. Various studies have established the association between the presence of FLD and an increased risk of HCC as well as both liver- and non-liver-related mortality.[1] Given the strong association between metabolic syndrome (MetS) and its components with FLD, screening for steatosis and/or advanced liver disease in patients with metabolic comorbidity is recommended by several guidelines.[2–6]

Screening strategies typically target persons with clinical risk factors for FLD or biochemical signs suggestive of liver disease.[3–6] Given that the prevalence of metabolic comorbidities is rapidly increasing, an increasing number of patients will become eligible for hepatic assessment. This is particularly relevant in the elderly because the majority will have at least one risk factor for FLD, and, among them, screening appears to be challenging because of poor performance of non-invasive tests in this group.[7–9]

Current guidelines that support screening would therefore necessitate an assessment of hepatic steatosis (HS) in the majority of elderly persons,[3–6] despite a paucity of evidence on the clinical relevance of FLD in this target population. Although FLD has been associated with mortality in several large studies, careful assessment of elderly subgroups in these cohorts revealed no association between the presence of FLD and excess mortality in this subset.[10–13] These studies, however, included only a limited number of elderly participants with FLD, and these findings therefore warrant further exploration.

Therefore, we investigated the relationship between FLD and mortality in an elderly population.

PARTICIPANTS AND METHODS

Study population

The Rotterdam Study is a large, prospective, population-based cohort study, which commenced in 1989, enrolling adults ≥ 45 years old residing in the Ommoord district of Rotterdam, The Netherlands. Since 2009, hepatic assessment was introduced as part of the regular visits. The rationale, study design, and recent findings have been summarized elsewhere.[14] For the current analysis, only participants visiting the research center between 2009 and 2014, ≥ 65 years old, with available data on hepatic ultrasound were included (Figure 1).

Liver stiffness and steatosis assessment

All enrolled persons underwent hepatic ultrasound by an experienced operator. Steatosis was assessed using established ultrasound criteria.[15] For sensitivity analyses, we also defined the presence of steatosis as a fatty liver index (FLI) ≥ 60.[16] Metabolic dysfunction-associated fatty liver disease (MAFLD) was defined as the presence of steatosis together with either overweight, diabetes, or presence of at least two minor criteria.[17] NAFLD was defined as the presence of steatosis in the absence of secondary causes comprising viral hepatitis, steatogenic drug use, or excessive alcohol consumption (> 20 g/d for females or >30 g/d for males).[2] Participants were excluded from NAFLD analysis if secondary causes for steatosis were present or could not be ruled out, in line with recent publications.[18]

Liver stiffness (LS) was measured using transient elastography (FibroScan; EchoSens, France, Paris), according to the manufacturer's instructions. Only measurements that complied with the criteria described by Boursier et al. were considered valid (interquartile range, <30% in the case of an LS measurement ≥ 7.0 kPa).[19] LS was subsequently categorized using a threshold of 8.0 kPa, which suggests fibrosis.[20]

Follow-up and mortality data

Mortality data were extracted from the municipal registries and were complete until January 1, 2018. Cause-specific mortality was obtained from medical records and complete until January 1, 2015. In addition to all-cause mortality, we also assessed the association between FLD and cancer-related mortality (comprising all neoplasms regardless of primary origin) and cerebro-cardiovascular mortality (comprising cerebrovascular, cardiovascular, and vascular events).

Covariates

Blood samples were acquired at each study visit. Performed tests included liver biochemistry, serum glucose, homeostatic model assessment for insulin
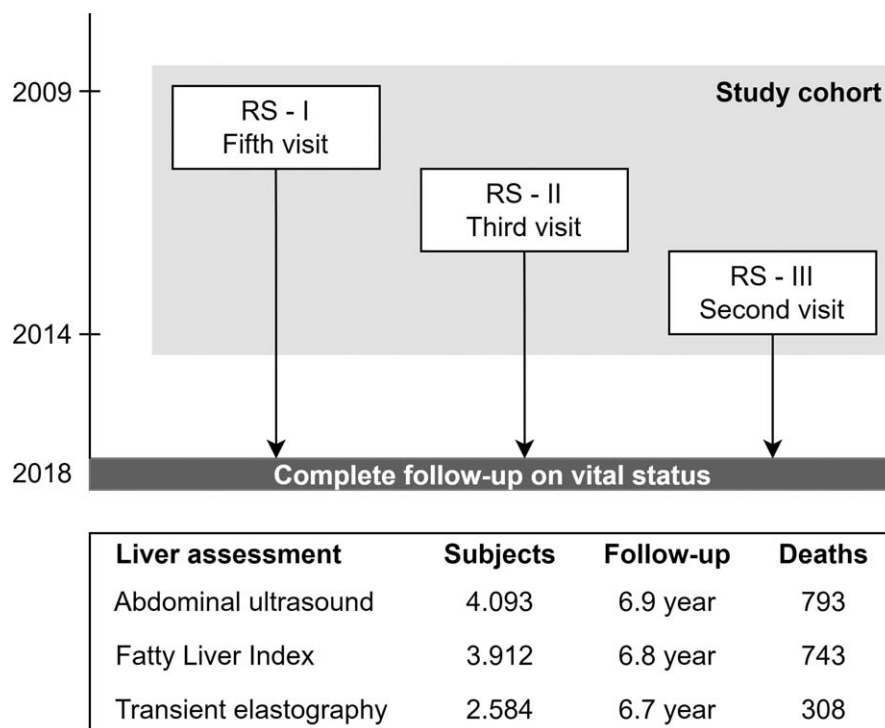
FIGURE 1 Overview of the Rotterdam Study subsets included in our study cohort. For the final cohort, RS-I, RS-II, and RS-III data were combined. Data originated from visits in 2009 until 2014 and follow up was complete until 2018.

resistance, and assessment of dyslipidemia. All participants underwent anthropomorphic measurements, including waist circumference. Medication data were obtained from direct linkage with pharmacy databases, with actual use verified during an interview. According to the Adult Treatment Panel (ATP)-III criteria, MetS was present if the participants complied with at least three of the following subcomponents[21]: (1) (pre) diabetes, defined as fasting glucose >5.6 mmol/L, antidiabetic drug use, or diagnosis of diabetes by health care professionals; (2) high waist circumference, defined as >102 cm in males or >88 cm in females; (3) hypertriglyceridemia, defined as triglycerides ≥ 1.7 mmol/L and/or lipid-lowering drug use; (4) hypo-HDL, defined as HDL < 1.04 mmol/L in males or <1.30 in females and/or lipid-lowering drug use; and (5) hypertension, defined as either systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg, and/or antihypertensive drug use.

Statistical analysis

Associations between baseline factors and mortality during follow-up were assessed using Cox proportional hazard regression. Associations between steatosis, NAFLD, MAFLD, and all-cause mortality were first explored in the overall population. The fully adjusted model comprised education, smoking, alcohol, the individual components of MetS (hypertension, [pre]

diabetes, high waist circumference, hypo-HDL, and hypertriglyceridemia), history of coronary heart disease, heart failure, and stroke, based on previous research in this cohort and clinical relevance.[22] Next, we assessed the association between steatosis and all-cause mortality across various subgroups, including age categories, sex, presence of MetS (and its individual components), presence of liver test abnormalities (according to local upper limit of normal), and history of cardiovascular disease (heart failure, stroke, or coronary heart disease).

Furthermore, we assessed the impact of body mass index (BMI) on the investigated associations in two ways. First, we included BMI as a covariate besides the already included covariates. Second, we stratified the main analysis for BMI categories (< 25, 25–30, and ≥ 30 kg/m²).

For additional sensitivity analyses, associations were further explored for mortality before and after 5 years of follow-up and for cause-specific mortality: (1) cancer mortality and (2) cerebro-cardiovascular mortality. Additionally, analyses were performed with the diagnosis of steatosis based on FLI instead of ultrasound. Finally, we assessed the association between LS (continuous and categorical) and mortality stratified for the presence of steatosis. Participants with a history of heart failure were excluded from these analyses because heart failure is associated with increased LS attributable to congestion.[23,24]

Analyses were performed using R software (version 4.0.4; R Foundation for Statistical Computing, Vienna,

Austria), using the *survival* package 3.2–10. A *p* value of <0.05 was considered statistically significant.

Ethics and participants involvement

The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus MC (registration no.: MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO; license no.: 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 World Health Organization International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalog number NTR6831. All participants provided written informed consent to participate in the study and have their information obtained from treating physicians. All authors had access to the study data and reviewed and approved the final manuscript. Participants were not involved in the research design and conduct.

RESULTS

General characteristics

We included 4093 elderly participants; mean age was 74.4 ± 6.6 years, 98.1% were of European ancestry, and 42.7% were male. Metabolic comorbidity was highly prevalent (e.g., diabetes, 18.0%; BMI, 27.6 ± 4.2 kg/m^2; MetS, 54.7%). This resulted in 85.4% ($n = 3.496$) of participants necessitating hepatic assessment for the presence of metabolic dysfunction according to the 2021 European Association for the Study of the Liver guideline on noninvasive tests.[3,17] Among the included participants, 36.8% had steatosis and 7.1% LS ≥ 8.0 kPa. Additional baseline characteristics are shown in Table 1. During the median follow-up duration of 6.9 years, 793 deaths were recorded, yielding a mortality rate of 29.6 per 1000 person-years. Among those with cause-specific mortality data ($n = 344$ of 793), 39.2% died because of cancer and 30.5% died because of cerebro-cardiovascular events; only 1 participant died because of a liver-related death. MAFLD was present in 1459 of 4089 (35.7%) participants after excluding 4 participants for insufficient data for classification, and NAFLD was present in 1148 of 3225 (35.6%) participants after excluding 868 participants with secondary causes for steatosis ($n = 611$) and/or insufficient data on alcohol consumption ($n = 266$).

Steatosis is not associated with all-cause mortality in the elderly

In our cohort, the presence of HS was not associated with a higher risk of death in fully adjusted models (adjusted HR [aHR], 0.87; 95% CI, 0.73–1.03; Figure 2). Similar results were obtained for MAFLD (aHR, 0.87; 95% CI, 0.73–1.03) and NAFLD (aHR, 0.89; 95% CI, 0.73–1.09). Findings were consistent using age- and sex-adjusted models or when the presence of steatosis was based on an FLI ≥ 60. Furthermore, similar associations were observed for mortality during the initial 5 years of follow-up (aHR, 0.85; 95% CI, 0.67–1.08) compared to the follow-up beyond 5 years (aHR, 0.89; 95% CI, 0.70–1.14; Table S1). Adding BMI to the final model did not affect our outcomes, but revealed that higher BMI—taking into account all other metabolic dysfunction criteria—was associated with reduced mortality risk (aHR, 0.94/kg/m^2; 95% CI, 0.92–0.97).

Steatosis is not associated with an increased risk of mortality: subgroup analysis

In line with the findings in the overall population, presence of HS was not associated with increased mortality risk across a range of prespecified subgroups, including age categories, sex, presence of diabetes or metabolic dysfunction, elevated liver enzymes, or history of cardiac disease, in models adjusted for age and sex (Figure S1) and in fully adjusted models (Figure 3). Interestingly, presence of HS was actually associated with a mildly reduced mortality risk among patients with hypertension, (pre)diabetes, and high waist circumference.

Similarly, when analyses were stratified for BMI, we confirmed our previous findings that the absence of steatosis in patients with metabolic dysfunction (in this case obesity) could be suspicious. Multivariable models indicated that steatosis was associated with reduced mortality risk among the obese (HR, 0.63; 95% CI, 0.45–0.90), whereas it did not affect mortality in overweight (HR, 0.99; 95% CI, 0.79–1.26) and normal weight (HR, 0.99; 95% CI, 0.68–1.44).

No association between steatosis and cancer-related mortality or cerebro-cardiovascular mortality

In multivariable analysis, presence of steatosis was not associated with cancer-related mortality (aHR, 0.77; 95% CI, 0.51–1.16) or cerebro-cardiovascular mortality (aHR, 0.90; 95% CI, 0.54–1.50). Of note, these HRs

TABLE 1 Participants' characteristics

Variable	All $n = 4093$	Steatosis $n = 1508$	No Steatosis $n = 2585$
Demographics			
Age (years)	74.4 (6.6)	73.7 (6.0)	74.8 (6.9)
Male	1749 (42.7)	661 (43.8)	1088 (42.1)
Education			
Low	2131 (52.8)	853 (57.6)	1278 (50.0)
Medium	1200 (29.7)	418 (28.2)	782 (30.6)
High	705 (17.5)	211 (14.2)	494 (19.3)
Current/former smoking	2766 (67.7)	1076 (71.6)	1690 (65.5)
Excessive alcohol intake	499 (13.0)	227 (16.1)	272 (11.3)
Physical examination			
Waist circumference (cm)			
Male	99.2 (10.8)	105.0 (10.3)	95.6 (9.4)
Female	89.8 (11.9)	97.1 (10.8)	85.6 (10.3)
BMI (kg/m^2)	27.6 (4.2)	29.9 (4.3)	26.3 (3.6)
Comorbidity			
Hypertension	3585 (87.8)	1387 (92.3)	2198 (85.1)
Diabetes	720 (18.0)	408 (27.8)	312 (12.4)
MetS	2193 (54.7)	1092 (74.0)	1101 (43.4)
Coronary heart disease	463 (11.3)	178 (11.8)	285 (11.0)
Heart failure	208 (5.1)	76 (5.0)	132 (5.1)
Biochemistry			
AST (U/L)	25 [21, 29]	25 [22, 29]	24 [21, 28]
ALT (U/L)	18 [14, 24]	21 [17, 27]	17 [14, 21]
FLI > 60	1404 (35.9)	893 (62.1)	511 (20.6)
Transient elastography			
LS (kPa)[a]	4.9 [4.0, 6.1]	5.3 [4.3, 6.7]	4.8 [4.0, 5.9]
LS ≥ 8.0 kPa[a]	183 (7.1)	110 (12.4)	73 (4.3)

Note: Data are presented as mean (SD), median [P25-P75], or n and percentage.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; P25-P75, 25th–75th percentile.
[a]Comprises only valid measurements in participants without heart failure.

were similar to those observed for all-cause mortality (aHR, 0.87; 95% CI, 0.73–1.03).

HS with LS ≥ 8.0 kPa is not associated with increased mortality

Valid LS measurements were available in a subset of participants ($n = 2584$; age, 72.7 ± 6.6; median follow-up = 6.7 years; mortality rate, 18.8 per 1000 person-years). Among those with steatosis, LS (aHR, 1.04 per kPa; 95% CI, 0.95–1.14) was not associated with mortality. Similar results were obtained among those without steatosis (aHR, 0.98 per kPa; 95% CI, 0.90–1.06). Even when those with both steatosis and LS ≥ 8.0 kPa were compared to those without steatosis and lower LS, no significant differences were observed in survival (aHR, 1.11; 95% CI, 0.65–1.89). Similar results were obtained when high LS was defined as 10.0 kPa.

DISCUSSION

In this large, ongoing prospective cohort comprising community-dwelling elderly persons with a median follow-up of 6.9 years, the presence of FLD was not associated with increased mortality. Consistent results were obtained across a range of clinically relevant subgroups. These findings indicate that hepatic assessment is unlikely to improve outcomes among the elderly.

FLD is a widely accepted risk factor for liver-related morbidity and mortality based on the results of various large cohort studies.[25] As a result, several guidelines recommend hepatic assessment to screen for the presence of FLD, particularly in those with metabolic dysfunction.[2–6] Given that most persons ≥ 65 years old have at least one metabolic risk factor, up to an alarming 85% of our study population would opt for hepatic health assessment according to these guidelines. However, the clinical relevance of HS and fibrosis in this elderly population is currently unclear.
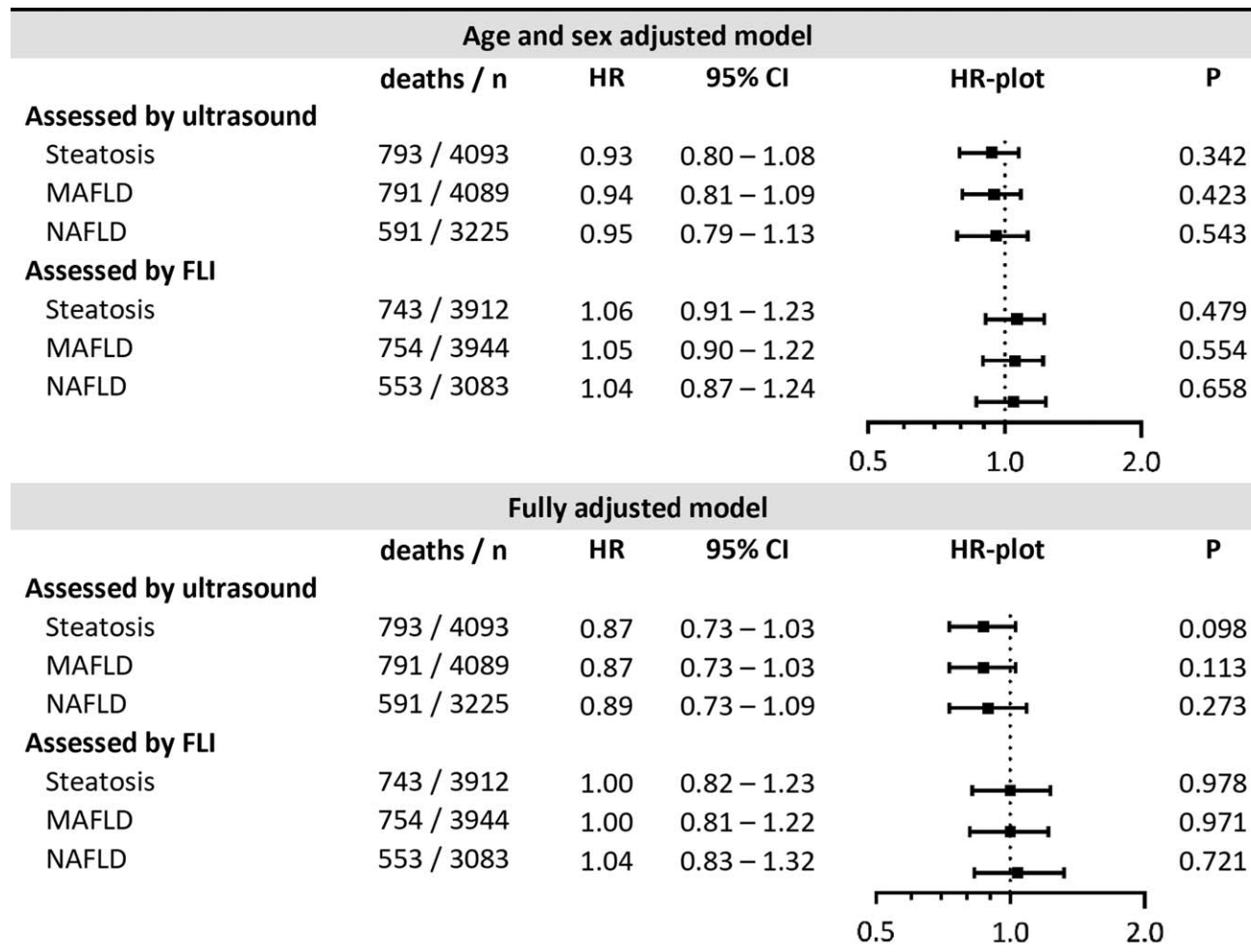
Age and sex adjusted model					
	deaths / n	HR	95% CI	HR-plot	P
Assessed by ultrasound					
Steatosis	793 / 4093	0.93	0.80 – 1.08		0.342
MAFLD	791 / 4089	0.94	0.81 – 1.09		0.423
NAFLD	591 / 3225	0.95	0.79 – 1.13		0.543
Assessed by FLI					
Steatosis	743 / 3912	1.06	0.91 – 1.23		0.479
MAFLD	754 / 3944	1.05	0.90 – 1.22		0.554
NAFLD	553 / 3083	1.04	0.87 – 1.24		0.658

0.5   1.0   2.0

Fully adjusted model					
	deaths / n	HR	95% CI	HR-plot	P
Assessed by ultrasound					
Steatosis	793 / 4093	0.87	0.73 – 1.03		0.098
MAFLD	791 / 4089	0.87	0.73 – 1.03		0.113
NAFLD	591 / 3225	0.89	0.73 – 1.09		0.273
Assessed by FLI					
Steatosis	743 / 3912	1.00	0.82 – 1.23		0.978
MAFLD	754 / 3944	1.00	0.81 – 1.22		0.971
NAFLD	553 / 3083	1.04	0.83 – 1.32		0.721

0.5   1.0   2.0

FIGURE 2 Mortality risk among elderly participants with steatosis, NAFLD and MAFLD. Results were obtained with Cox regression analysis. The age- and sex-adjusted model was only adjusted for age and sex; the fully adjusted model was, in addition, adjusted for education, smoking, alcohol, the individual components of MetS (hypertension, [pre]diabetes, hypo-HDL, hypertriglyceridemia, and high waist circumference), heart failure, coronary heart disease, and stroke.

In the current study, FLD (steatosis, MAFLD, and NAFLD) was not a risk factor for mortality. These findings align with a recent study, demonstrating that the clinical relevance of FLD attenuates as age increases.[13] Our results were consistent across all subgroups, across different periods of follow-up, and for both cancer-related and cerebro-cardiovascular mortality. Furthermore, even patients with both steatosis and elevated LS (suggestive of liver fibrosis) were not at an increased risk of death.

There are several explanations to account for the differences observed in our cohort when compared to previously published data. First, liver-related death is uncommon among community-dwelling elderly given that the majority of patients developing end-stage liver disease do so at a younger age. For example, the average age for NASH is 40–50 years and NASH-cirrhosis 50–60 years,[4] in line with the mean age for NASH-related liver transplantation in the USA (59 years).[26] Second, the participants enrolled in this cohort, that is, the community-dwelling elderly able to visit the research center, may represent a healthy subset; a phenomenon related to survival bias. This is further illustrated by the rather low median LS, even among those with elevated LS; median LS was only 9.2 kPa. This indicates that cirrhosis is rare in the elderly general population, unlike fibrosis.

Another potential confounder is weight loss. As described previously, only a minor decrease in body fat percentage results in rather large improvements of liver fat or hepatic triglycerides, even while adiposity persists.[27,28] To further complicate matters, weight loss is an important predictor for impaired survival among the elderly. Weight loss might thus facilitate steatosis regression and also predict mortality. This might explain why the presence of steatosis was associated with a reduced risk of mortality in those with metabolic dysfunction (e.g., high waist circumference, hypertension, and prediabetes) or obesity, in whom steatosis is expected and could be conspicuous when absent. In
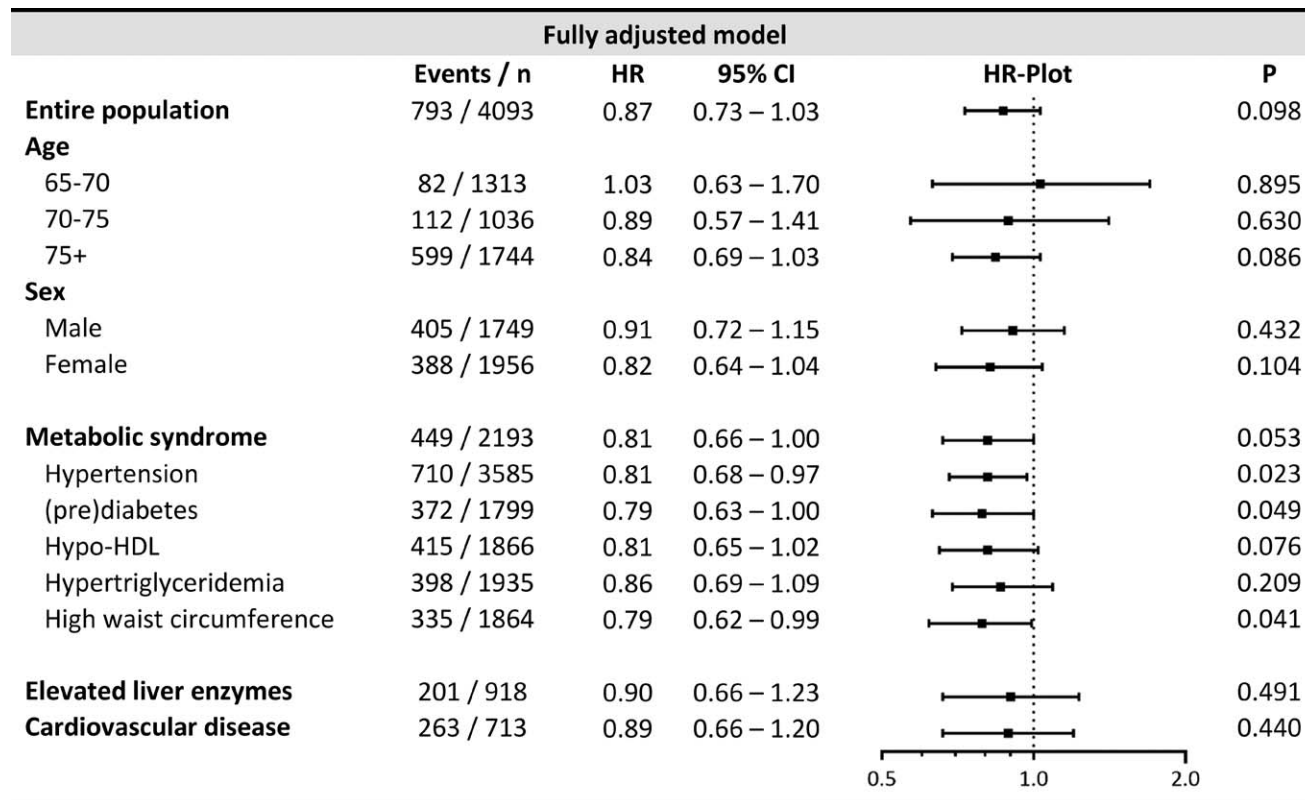
Fully adjusted model					
	Events / n	HR	95% CI	HR-Plot	P
Entire population	793 / 4093	0.87	0.73 − 1.03		0.098
Age					
65-70	82 / 1313	1.03	0.63 − 1.70		0.895
70-75	112 / 1036	0.89	0.57 − 1.41		0.630
75+	599 / 1744	0.84	0.69 − 1.03		0.086
Sex					
Male	405 / 1749	0.91	0.72 − 1.15		0.432
Female	388 / 1956	0.82	0.64 − 1.04		0.104
Metabolic syndrome	449 / 2193	0.81	0.66 − 1.00		0.053
Hypertension	710 / 3585	0.81	0.68 − 0.97		0.023
(pre)diabetes	372 / 1799	0.79	0.63 − 1.00		0.049
Hypo-HDL	415 / 1866	0.81	0.65 − 1.02		0.076
Hypertriglyceridemia	398 / 1935	0.86	0.69 − 1.09		0.209
High waist circumference	335 / 1864	0.79	0.62 − 0.99		0.041
Elevated liver enzymes	201 / 918	0.90	0.66 − 1.23		0.491
Cardiovascular disease	263 / 713	0.89	0.66 − 1.20		0.440

0.5   1.0   2.0

FIGURE 3 Mortality risk among elderly participants with steatosis: subgroup analysis. Results were obtained with Cox regression analysis. The fully adjusted model was adjusted for age, sex, education, smoking, alcohol, the individual components of MetS (hypertension, [pre]diabetes, hypo-HDL, hypertriglyceridemia, and high waist circumference), heart failure, coronary heart disease, and stroke.

fact, additionally adjusting for BMI in the final models revealed that higher BMI (in light of all other confounders) was associated with lower mortality risk. This phenomenon is in line with the so-called obesity paradox and concepts of reverse causality.[29]

Our findings have very important clinical implications. Screening for FLD is recommended by a range of guidelines, especially among those with metabolic dysfunction.[2–5] Such risk factors were present in up to 85% of this elderly study population, resulting in a vast number of community-dwelling elderly adults as potentially eligible for hepatological assessment. However, the current study indicates that such screening strategies may not be warranted in the elderly, given that the first of Wilson and Jungner's criteria, namely that the condition should be an important health problem, is violated in elderly subjects.[30] Therefore, screening for FLD and/or fibrosis is unlikely to improve outcomes among the elderly and is not recommended.

It is, however, essential to note that our findings cannot be applied to younger populations, given that in those cohorts the disease burden of FLD increased drastically over the past decades.[31,32] For example, FLD is already one of the major indications for liver transplant in the USA.[33] Rather, our findings highlight that policies to limit the disease burden of FLD should focus on the young- to middle-aged population and not the elderly.

LIMITATIONS

This is the largest study to date on the association between FLD and mortality in the elderly, but the following limitations should be considered. First, this cohort is almost entirely of European ancestry (98%), and results should be confirmed among multiethnic populations. Second, the median follow-up is limited to 6.9 years. Nonetheless, 749 events occurred, and given the large sample size, a total of 26,765 person-years of follow-up was obtained. Moreover, in additional analyses, we observed no differences in hazard rates before and after 5 years of follow-up, suggesting the limited impact of the follow-up duration on our results. Third, one can argue that FLD was not associated with increased risk of mortality, given that the multivariable models included many parameters closely related to FLD itself. However, it is unlikely that this affected any of our conclusions because results were consistent in additional analysis when only adjusted for age and sex. Fourth, because data on liver-related events are not available in this cohort, these could not be addressed in our analyses. Finally, the gold standard for assessing

steatosis and fibrosis remains liver biopsy, which is invasive and prone to sampling error.[34] However, because ultrasound-based diagnosis is operator dependent, we confirmed our results through sensitivity analyses using an FLI-based definition of steatosis. Unfortunately, both modalities cannot distinguish between different steatosis grades reliably. Therefore, additional research using controlled attenuation parameter or MRI/proton density fat fraction to quantify steatosis severity by a continuous assessment is warranted to investigate the association between steatosis severity and mortality.

In this large cohort of adults ≥ 65 years old, the presence of FLD was not associated with increased mortality, whereas a worrisome 85% of this group necessitated hepatic assessment according to recent guidelines. Findings were consistent across a range of clinically relevant subgroups. These findings do not support the currently recommended screening for FLD and/or fibrosis among the elderly population.

AUTHOR CONTRIBUTIONS

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FUNDING INFORMATION

CONFLICTS OF INTEREST

Robert J. de Knegt consults for and received grants from AbbVie. He is on the speakers' bureau for Echosens. He received grants from Gilead and Janssen.

DISCLOSURES

M.J.S. has received speaker's fees and research support from Fujirebio and received grants from Gilead. R.dK. is a speaker for Echosens, a consultant for AbbVie, and received grants from AbbVie, Gilead, and Janssen. Other authors had no conflict of interest.

DATA AVAILABILITY STATEMENT

Data can be obtained upon request. Requests should be directed toward 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.

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