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Metabolic dysfunction-associated steatotic liver disease as a predictor of cognitive performance: An 11-year population-based follow-up study

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ABSTRACT

Background: Prevalent manifestation of metabolic dysfunction, metabolic dysfunction-associated steatotic liver disease (MASLD), has been associated with poorer cognitive performance and greater decline in cognitive functions.
Aim: The aim of this study was to analyze whether MASLD, measured by fatty-liver-index (FLI), predicts decline in cognitive performance during 11 years.
Methods: This study was based on the Finnish nationwide, population-based Health 2000 Health Examination Survey and its follow-up, Health 2011 Survey. Cognitive performance was assessed with verbal fluency, word-list learning (WLL), delayed word-list recall (both at baseline and at follow-up), and with simple reaction time and visual choice reaction time tests (only at baseline). Statistical analyses were performed using multivariate linear regression adjusted for age, sex, education, *APOE* $\varepsilon 4$ genotype, hypercholesterolemia, diabetes mellitus, hypertension, depressive symptoms, physical activity smoking status, C-reactive protein and HOMA of insulin resistance.
Results: Cross-sectionally, 5,139 (mean age 52.3 years) and longitudinally, 3,143 (mean age 49.3 years) participants were examined. Cross-sectionally, no associations between FLI and cognitive performance were found in the adjusted models. Longitudinally, baseline FLI > 60 predicted poorer WLL ($p < 0.005$) and a decline in WLL from baseline to follow-up ($p < 0.04$).
Conclusions: Our results suggest that MASLD is an independent predictor of decline in a test measuring working memory and learning.

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly non-alcoholic fatty liver disease, is a common disease with prevalence estimated to be 25 % [1]. It has been suggested that MASLD could contribute to or act as an independent risk factor for cognitive decline [2–6]. However, a clear connection is difficult to decipher as etiologies of both MASLD and cognitive decline are multifactorial and ample, and the development of these conditions take time. Moreover, these conditions have similar risk factors, such as obesity, type 2 diabetes mellitus (T2DM), hyperlipidemia, hypertension and metabolic syndrome [1,7–10]. Many of these comorbidities are associated with low-grade inflammation, insulin resistance (IR) and risk of cerebral hypoperfusion.

Population-based cross-sectional studies have found significant associations between MASLD and poorer cognitive performance in young and middle-aged adults [2,3,11–16], and in people over 60

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years [17]. However, scarce evidence for a longitudinal association exists.

We hypothesized that MASLD, measured by fatty liver index (FLI), would associate with poorer cognitive performance cross-sectionally and with cognitive decline longitudinally. To test this hypothesis, we analyzed the associations between MASLD and cognitive performance cross-sectionally; the association between baseline MASLD and follow-up cognitive performance; and the change in test scores after an 11-year follow-up period in a representative sample of Finnish adult population. Adjustments were made for cardiovascular, metabolic and inflammatory factors.

2. Materials and methods

2.1. Study design and participants

The Health 2000 and 2011 surveys were conducted by Finnish Institute for Health and Welfare in the years 2000–2001 and 2011–2012. The study sample of 8028 individuals was a representative sample of the Finnish adult population in the year 2000. From the study sample of Health 2000, everyone who had not died, refused to participate in further surveys or moved abroad was invited to the Health 2011 survey [18].

The plan and protocols of the Health 2000 and 2011 surveys were approved by the Ethics Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa. All participants gave written informed consent before attending the surveys [19].

Those that did not attend the health examination proper and who had fasted less than 4 hours before blood tests were excluded from this study [20]. In the diagnostic criteria for MASLD, alcohol consumption should not exceed 20 and 30 grams per day for women and men, respectively [21]. Concordantly, those with excessive or unknown alcohol usage were excluded. Also, participants with missing variables needed to calculate the FLI value and those who did not attend cognitive testing at baseline were excluded. Cross-sectional analyses were performed with this study population. Those from the cross-sectional analyses who also attended the follow-up cognitive testing were included in the longitudinal analyses. A detailed flow-chart of the study population is presented in Fig. 1.

2.2. Covariates

Body-mass-index (BMI) was measured by dividing weight (kg) by the square of height (m) [19]. Waist circumference (WC) was measured with an accuracy of 0.5 cm [20]. Level of alcohol consumption was obtained *via* a questionnaire and an approximation for daily alcohol consumption was calculated (g/day). Depressive symptoms were evaluated with Beck's depression inventory (BDI) [22]. Years of formal education and current smoking status were retrieved from interview data [19]. Level of physical activity was assessed with a questionnaire. The participants were asked how often they exercise at least 30 minutes with enough intensity to cause mild sweating and breathlessness. The results were classified as follows: 1=a few times a year or more seldom, 2 = 2–3 times a month, 3 = once a week, 4 = 2–3 times a week, 5 = 4–6 times a week, and 6 = daily. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or using anti-hypertensive medication [18]. DM status of subjects was determined by the usage of any DM medication or having fasting glucose value >7.0 mmol/l. Hypercholesterolemia was defined as the usage of any lipid-lowering agent or having serum total cholesterol value >6.5 mmol/l. Apolipoprotein E (*APOE*) genotype was defined from participants that gave consent for DNA sampling, and participants were classified as either carriers or non-carriers of *APOE* $\varepsilon 4$ allele.

From venous blood samples, concentrations of glucose, triglyceride, total cholesterol, gamma-glutamyl transferase (GGT), high-sensitivity C-reactive protein (hs-CRP) and insulin were determined. Further, IR was estimated with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). HOMA-IR was counted by multiplying fasting insulin (μU/ml) with fasting glucose (mmol/l) and dividing by 22.5 [23].

2.3. Cognitive tests

Cognitive tests were derived from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery. At baseline, verbal fluency (VF), word-list learning (WLL), delayed word-list recall (DWLR), and simple and visual choice reaction times (SRT and VCRT) were tested. At follow-up, subjects were tested for VF, WLL and DWLR. These tests represent language skills and executive functions, verbal learning and memory, and episodic memory, respectively [24]. Performance of these tests is described elsewhere [19].

2.4. Fatty liver index

MASLD was defined with FLI, an equation that considers BMI, WC, and concentrations of GGT and triglycerides (Formula 1).

If FLI is less than 30, MASLD is unlikely [25]. FLI over 60 makes MASLD a likely diagnosis [25,26]. Those with FLI 30–60 are considered having an intermediate risk for MASLD [26].

$$FLI = \frac{e^{0.953\times\log_e(triglycerides)+0.139\times BMI+0.718\times\log_e(GGT)+0.053\times WC-15.745}}{1+e^{0.953\times\log_e(triglycerides)+0.139\times BMI+0.718\times\log_e(GGT)+0.053\times WC-15.745}}\times 100$$

Formula 1. Equation for calculating fatty liver index. FLI=fatty liver index; BMI=body-mass index; GGT=gamma-glutamyl-transferase (U/l); WC=waist circumference (cm).

2.5. Statistical analysis

To examine characteristics of the FLI groups, subjects were divided into groups of FLI < 30, FLI 30–60 and FLI > 60. For continuous variables, one-way ANOVA was used, and Tukey's honest significance test (HSD) was utilized to evaluate pair-wise differences between the FLI groups. Chi-square test was used for categorical variables.

Differences between the FLI groups in cognitive test scores were analyzed by linear models, followed by pairwise comparisons with Tukey's HSD if there was a significant overall difference among the three groups. Bonferroni correction for multiple comparisons was performed by multiplying uncorrected p values by the number of cognitive tests (5 at baseline, 3 at follow-up). Based on different characteristics of the FLI groups and known factors that affect cognition according to literature, adjustments were made in three models. Model 1 was adjusted for sex, age and years of education. Model 2 was adjusted for Model 1+hypertension, hypercholesterolemia, DM and *APOE* $\varepsilon 4$ carriership. Model 3 was further adjusted for Model 2+BDI score, physical activity and smoking status. Additionally, adjustments were made for HOMA-IR in Model 2 since IR has been shown to associate with cognitive decline [27,28]. Similarly, the effect of low-grade inflammation was examined by adjusting for hs-CRP in Model 2 [15]. The change in cognitive test performance during the follow-up period was calculated by subtracting the baseline test result from the follow-up test result. In the analysis of change in cognitive tests, all models were adjusted for baseline cognitive test score. In addition, a

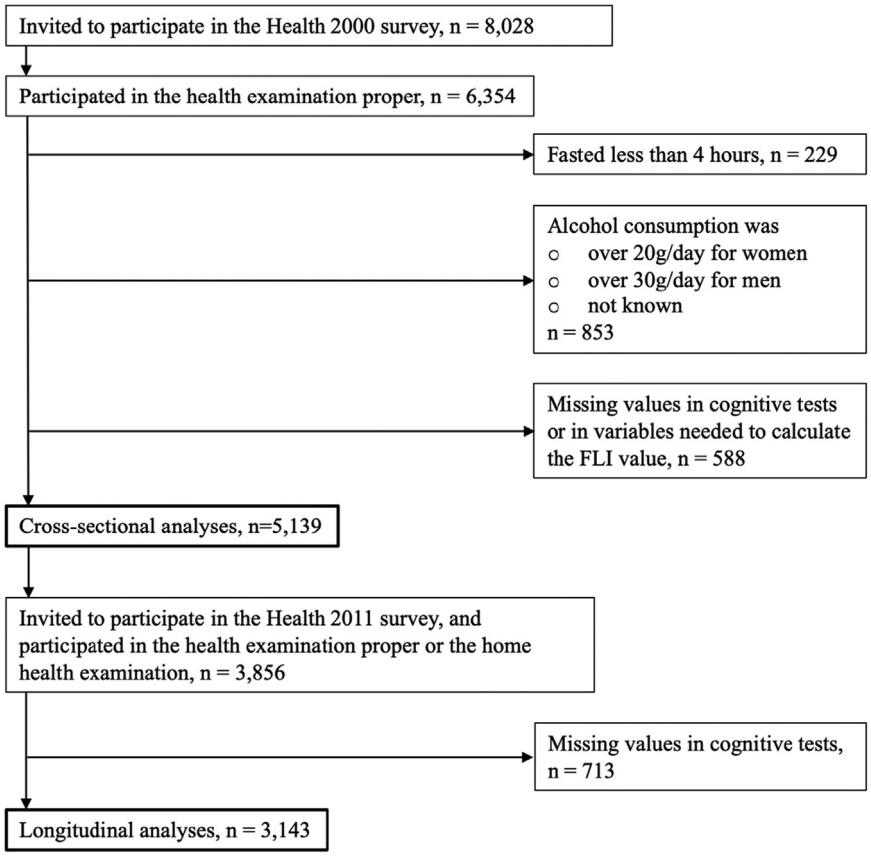

Fig. 1. Flow-chart of the study population. Abbreviations: FLI=fatty liver index.

global cognitive score was calculated by standardizing each cognitive test score to the mean and standard deviation of the baseline study population and calculating a mean value of the z-scores. Before the calculation of z-scores of SRT and VCRT, the values were multiplied by -1 to determine their additive inverses since longer response time reflects a worse result. Analyses for cross-sectional and longitudinal associations between FLI and global cognitive z-score were performed in Models 1 and 2. Additionally, change in global cognitive z-score was determined by subtracting the baseline result from the follow-up result. The association between FLI and change in cognitive z-score was analyzed in Models 1 and 2, and the Models were adjusted for baseline global cognitive score.

In addition to categorical analyses, FLI was also treated as a continuous variable. The analyses were performed first for all participants and then additionally, to study the effect of low to intermediate FLI value on cognition, those with FLI > 60 were excluded from the analyses.

BDI score, HOMA-IR, FLI, hs-CRP, SRT and VCRT were skewed to the right, so to achieve normal distribution, a logarithmic transformation ($\log_e$) was used. $P = 0.05$ (two-tailed) was set as the level of significance. Statistical software used was SAS JMP Pro 17.0.0 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of study participants

The baseline characteristics of the participants of longitudinal analyses are shown in Table 1. Of these 3143 participants, 311 had FLI value over 60. The participants with FLI > 60 were older and less educated and more often male than female compared to FLI < 30. Levels of HOMA-IR and hs-CRP were higher in the participants with FLI > 60. Also, the prevalence of DM, hypertension and hypercholesterolemia were higher in the group with FLI > 60. Those with FLI > 60 seemed to exercise more compared to those with FLI < 30. Prevalences of *APOE* ε4 carriership and smoking were similar in all groups. For baseline scores in cognitive tests, SRT and VCRT were slower and VF, WLL and DWLR scores lower in the group with FLI > 60. Global cognitive z-scores were lower among those with FLI > 60 compared to those with FLI < 30. The characteristics for those included only in the cross-sectional analyses were similar (Table S1).

Compared to those who were excluded from the cross-sectional analyses (Fig. 1), the participants who were included in the present study were older ($p < 0.0001$) and were more educated ($p < 0.0001$). Those who were included in this study were more often female than male (58.7 %, $p < 0.0001$).

The participants that were included in both cross-sectional and longitudinal analyses were younger ($p < 0.0001$) and had more years of formal education ($p < 0.0001$) than those who attended only the baseline examination. There was no difference between the proportion of men and women ($p = 0.94$).

Values are mean values (SD) unless stated otherwise. Significance of difference between FLI classes is assessed with ANOVA for continuous variables and with Chi-square test for categorical variables. Pairwise differences were analyzed with Tukey's HSD test when appropriate. Abbreviations: SD=standard deviation; FLI=fatty liver index; BDI=Beck's depression inventory; hs-CRP=high-sensitivity C-reactive protein; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance; DM=diabetes mellitus; ms=millisecond.

Table 1
Baseline characteristics and follow-up cognitive test scores of the study population who attended the follow-up examinations.

Variable	FLI < 30 n = 2329	FLI 30–60 n = 503	FLI > 60 n = 311	*P*-value ANOVA/Chi-square	*P*-value Tukey's HSD comparing FLI > 60 to FLI < 30	*P*-value Tukey's HSD comparing FLI > 60 to FLI 30–60
Sex, female n (%) n = 3143	1508 (64.5)	232 (45.9)	111 (35.6)	<0.0001		
Age (years) n = 3143	48.2 (12.1)	53.4 (11.6)	51.1 (11.1)	<0.0001	<0.0001	0.009
Years of education n = 3125	12.4 (4.0)	11.0 (3.7)	10.9 (3.5)	<0.0001	<0.0001	0.8
Carriership of *APOE* ε4 allele, n (%) n = 3024	718 (31.9)	151 (31.1)	99 (33.0)	0.9		
BDI score n = 3130	6.0 (6.1)	6.8 (6.7)	7.9 (7.2)	<0.0001	<0.0001	0.08
Alcohol consumption (g/day) n = 3143	5.2 (6.4)	6.1 (7.4)	6.4 (7.4)	0.0006	0.007	0.8
Current smoking, n (%) n = 3136	409 (17.5)	61 (12.1)	54 (17.3)	0.01		
Physical activity, higher value indicates more exercise n = 3126	3.3 (1.3)	3.4 (1.4)	3.6 (1.4)	<0.0001	<0.0001	0.03
Hypercholesterolemia, n (%) n = 3143	140 (6.0)	60 (11.9)	42 (13.5)	<0.0001		
HOMA-IR n = 3141	1.5 (1.1)	2.7 (1.6)	4.5 (6.6)	<0.0001	<0.0001	<0.0001
DM, n (%) n = 3143	22 (0.9)	25 (5.0)	32 (10.3)	<0.0001		
Hypertension, n (%) n = 3132	709 (30.4)	310 (61.8)	223 (71.9)	<0.0001		
hs-CRP (mg/l) n = 3124	1.4 (4.0)	2.1 (3.4)	3.5 (5.8)	<0.0001	<0.0001	<0.0001
Cognitive test scores in 2000						
Simple reaction time (ms) n = 3067	31.3 (6.3)	32.2 (6.7)	33.5 (8.5)	<0.0001	<0.0001	0.02
Visual choice reaction time (ms) n = 3024	45.1 (10.4)	46.7 (11.1)	47.1 (10.9)	0.0002	0.005	0.8
Verbal fluency score n = 3143	25.5 (6.9)	23.9 (6.8)	23.3 (6.9)	<0.0001	<0.0001	0.2
Word-list learning score n = 3143	22.0 (3.8)	21.0 (3.8)	20.5 (4.0)	<0.0001	<0.0001	0.1
Word-list delayed recall score n = 3143	7.6 (1.7)	7.2 (1.7)	7.0 (1.9)	<0.0001	<0.0001	0.7
Global cognition z-score n = 3022	0.3 (0.6)	0.1 (0.5)	0.006 (0.6)	<0.0001	<0.0001	0.07
Cognitive test scores in 2011						
Verbal fluency score n = 3143	24.7 (7.5)	22.6 (6.8)	22.6 (7.3)	<0.0001	<0.0001	1.0
Word-list learning score n = 3143	21.6 (4.4)	20.4 (4.4)	19.5 (4.5)	<0.0001	<0.0001	0.02
Word-list delayed recall score n = 3143	7.4 (2.1)	6.8 (2.1)	6.6 (2.2)	<0.0001	<0.0001	0.3
Global cognition z-score n = 3143	0.2 (0.9)	-0.1 (0.8)	-0.2 (0.9)	<0.0001	<0.0001	0.3

Values are mean values (SD) unless stated otherwise. Significance of difference between FLI classes is assessed with ANOVA for continuous variables and with Chi-square test for categorical variables. Pairwise differences were analyzed with Tukey's HSD test when appropriate. Abbreviations: APOE=apolipoprotein E; BDI=Beck's depression inventory; DM=diabetes mellitus; FLI=fatty liver index; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance; hs-CRP=high-sensitivity C-reactive protein; HSD=honest significance test; ms=millisecond.

3.2. Cross-sectional associations between fatty-liver-index and cognitive performance

Cross-sectional analyses were performed among the participants who attended the Health 2000 survey (n = 5139, Table 2 and S2). The association between MASLD and cognition was first analyzed by treating FLI as a categorical variable (Table 2). There was a difference between the FLI groups in VF in Models 1 and 2 (Model 1 p = 0.03, Model 2 p = 0.01), but not in Model 3 (p = 0.052). The difference was found between those with FLI > 60 and FLI < 30 in Model 1 (p = 0.01), Model 2 (p = 0.01) and Model 2+hs-CRP (p = 0.04). These differences did not survive Bonferroni correction (all p > 0.06). Additionally, an overall difference was found between the FLI groups in SRT in Model 1 (p = 0.002) and Model 2 (p = 0.02), but not in Model 3 (p = 0.07). FLI > 60 was associated with a slower SRT in Model 1 (p = 0.002, Bonferroni-corrected p = 0.02, compared to FLI < 30), and in Model 2 (p = 0.02, Bonferroni-corrected p = 0.1).

Treating FLI as a continuous variable resulted in FLI associating with slower SRT (Model 1 and 2 p < 0.05) but was lost after further adjusting in Model 3. In the analyses for continuous FLI, when those with FLI > 60 were removed, the association was lost (Table S2).

Participants with cross-sectional data at baseline were included in these analyses (n = 5139). Differences between groups was analyzed with linear models and post hoc pairwise comparisons were performed with Tukey's HSD. Values are weighted means (95 % CI). In model 1, adjustments were made for age, sex and years of education. Model 2 included adjustments for Model 1 + hypertension, DM, hypercholesterolemia and *APOE* ε4

Table 2
Adjusted means and 95 % confidence intervals of baseline cognitive test scores according to fatty liver index groups.

	FLI < 30, n = 3631	FLI 30–60, n = 885	FLI > 60, n = 623	*P* value ANOVA	*P*-value Tukey's HSD when comparing FLI > 60 to FLI 30–60	*P*-value Tukey's HSD when comparing FLI > 60 to FLI < 30	Bonferroni-corrected *P*-value Tukey's HSD when comparing FLI > 60 to FLI < 30
Model 1							
Verbal fluency	23.8 (23.5 to 24.0)	23.4 (23.0 to 23.9)	23.0 (22.5 to 23.5)	**0.03**	0.4	**0.03**	0.1
Word-list learning	20.5 (20.4 to 20.6)	20.5 (20.3 to 20.8)	20.3 (20.0 to 20.5)	0.2			
Delayed word-list recall	7.0 (6.9 to 7.0)	7.0 (6.9 to 7.1)	6.9 (6.8 to 7.0)	0.2			
Simple rection time	-1.14 (-1.15 to -1.14)	-1.13 (-1.14 to -1.12)	-1.11 (-1.13 to -1.10)	**0.002**	0.3	**0.002**	**0.01**
Visual choice reaction time	-0.77 (-0.78 to -0.76)	-0.76 (-0.77 to -0.74)	-0.76 (-0.78 to -0.74)	0.3			
Model 2							
Verbal fluency	23.8 (23.3 to 24.4)	23.5 (22.9 to 24.1)	23.0 (22.3 to 23.6)	**0.01**	0.3	**0.01**	0.06
Word-list learning	20.4 (20.0 to 20.7)	20.3 (20.0 to 20.7)	20.0 (19.7 to 20.4)	0.2			
Delayed word-list recall	6.9 (6.7 to 7.0)	6.9 (6.8 to 7.1)	6.8 (6.6 to 6.9)	0.3			
Simple rection time	-1.13 (-1.15 to -1.11)	-1.12 (-1.14 to -1.09)	-1.10 (-1.13 to -1.08)	**0.02**	0.5	**0.02**	0.1
Visual choice reaction time	-0.76 (-0.78 to -0.74)	-0.75 (-0.77 to -0.73)	-0.76 (-0.78 to -0.73)	0.5			
Model 3							
Verbal fluency	23.6 (23.0 to 24.3)	23.5 (22.8 to 24.2)	22.9 (22.1 to 23.6)	0.05			
Word-list learning	20.1 (19.7 to 20.4)	20.1 (19.7 to 20.5)	19.7 (19.3 to 20.2)	0.2			
Delayed word-list recall	6.8 (6.6 to 6.9)	6.9 (6.7 to 7.1)	6.7 (6.5 to 6.9)	0.1			
Simple rection time	-1.12 (-1.14 to -1.10)	-1.11 (-1.13 to -1.08)	-1.10 (-1.13 to -1.08)	0.07			
Visual choice reaction time	-0.75 (-0.78 to -0.73)	-0.75 (-0.78 to -0.73)	-0.75 (-0.78 to -0.73)	0.7			
Model 2 +HOMA-IR							
Verbal fluency	24.0 (23.4 to 24.5)	23.9 (23.2 to 24.6)	23.6 (22.9 to 24.4)	0.6			
Word-list learning	20.4 (20.1 to 20.7)	20.4 (20.1 to 20.8)	20.2 (19.8 to 20.6)	0.5			
Delayed word-list recall	6.9 (6.7 to 7.0)	6.9 (6.8 to 7.1)	6.8 (6.6 to 7.0)	0.3			
Simple rection time	-1.13 (-1.15 to -1.11)	-1.12 (-1.14 to -1.10)	-1.11 (-1.14 to -1.09)	0.2			
Visual choice reaction time	-0.76 (-0.78 to -0.74)	-0.76 (-0.78 to -0.74)	-0.76 (-0.79 to -0.74)	0.7			
Model 2 +hs-CRP							
Verbal fluency	23.8 (23.2 to 24.3)	23.4 (22.8 to 24.1)	23.0 (22.3 to 23.7)	**0.04**	0.4	**0.04**	0.2
Word-list learning	20.2 (19.9 to 20.5)	20.2 (19.9 to 20.6)	20.0 (19.6 to 20.4)	0.5			
Delayed word-list recall	6.8 (6.7 to 6.9)	6.9 (6.7 to 7.0)	6.8 (6.6 to 6.9)	0.5			
Simple rection time	-1.12 (-1.14 to -1.11)	-1.11 (-1.13 to -1.09)	-1.10 (-1.13 to -1.08)	0.1			
Visual choice reaction time	-0.76 (-0.78 to -0.74)	-0.75 (-0.77 to -0.73)	-0.76 (-0.78 to -0.73)	0.7			

Participants with cross-sectional data at baseline were included in these analyses (n = 5139). Differences between groups was analyzed with linear models and post hoc pairwise comparisons were performed with Tukey's HSD. Values are weighted means (95 % CI). In model 1, adjustments were made for age, sex and years of education. Model 2 included adjustments for Model 1 + hypertension, DM, hypercholesterolemia and *APOE* ε4 carriership. Model 3 was adjusted for Model 2 + BDI score, physical activity and smoking status. Additional adjustments were made separately for HOMA-IR and hs-CRP in Model 2. HOMA-IR, hs-CRP, simple and visual choice reaction times, and BDI scores were treated with natural logarithm to achieve a normal distribution. Abbreviations: *APOE*=apolipoprotein E; BDI=Beck's depression inventory; DM=diabetes mellitus; FLI=fatty liver index; HOMA-IR=homeostatic model assessment of insulin resistance; hs-CRP=high-sensitivity C-reactive protein; HSD=honest significance test. Bonferroni-corrected *P*-values (uncorrected *P*-value*5, not performed on *P*-value from ANOVA).

carriership. Model 3 was adjusted for Model 2 + BDI score, physical activity and smoking status. Additional adjustments were made separately for HOMA-IR and hs-CRP in Model 2. HOMA-IR, hs-CRP, simple and visual choice reaction times, and BDI scores were treated with natural logarithm to achieve a normal distribution. Abbreviations: *APOE*=apolipoprotein E; BDI=Beck's depression inventory; DM=diabetes mellitus; FLI=fatty liver index; HOMA-IR=homeostatic model assessment of insulin resistance; hs-CRP=high-sensitivity C-reactive protein; HSD=honest significance test. [a]*p*-value refers to overall difference between groups. Bonferroni-corrected *P*-values (uncorrected *P*-value*5 not performed on *P*-value from ANOVA). *$p < 0.05$ when comparing to FLI < 30.

3.3. Fatty-liver-index as a predictor for cognitive performance after 11 years

The association between baseline MASLD and cognitive performance at follow-up was analyzed first by treating FLI as a categorical variable (Table 3). Baseline FLI group predicted WLL at follow-up (all Models overall p < 0.005). Those with FLI > 60 at baseline had poorer WLL scores at follow-up when compared to those with FLI < 30 (all Models p < 0.02, Bonferroni-corrected $p < 0.05$, except for Model 2+HOMA-IR Bonferroni-corrected p = 0.1) and FLI 30–60 (all Models p < 0.003, Bonferroni-corrected $p < 0.009$).

Participants that attended both the Health 2000 and Health 2011 surveys were included in these analyses (n = 3143). Pairwise comparisons with Tukey's HSD were used to analyze differences between groups. Values are weighted means (95 % confidence intervals). In model 1, adjustments were made for age, sex and education. Model 2 included adjustments for Model 1 + hypertension, DM, hypercholesterolemia and *APOE* ε4 carriership. Model 3 was further adjusted for BDI score, physical activity and smoking status. Additional adjustments were made separately for HOMA-IR and hs-CRP in Model 2. FLI, HOMA-IR, hs-CRP, and BDI scores were treated with natural logarithm to achieve a normal distribution. Abbreviations: β=estimate; SE=standard error; FLI=fatty liver index; BDI=Beck's depression inventory; hs-CRP=high-sensitivity C-reactive protein; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance; DM=diabetes mellitus. Bonferroni-corrected *P*-values (uncorrected *P*-value*3, not performed on *P*-value from ANOVA).

Effect of continuous baseline FLI was also examined (Table S3). Higher FLI predicted poorer VF in Model 1 (estimate β = -0.3 (standard error 0.1), $p = 0.02$) and WLL (β = -0.1 (0.05), $p = 0.03$). However, these associations were no longer found after further adjustments (all p > 0.1 for VF and p > 0.07 for WLL). Additionally, these associations were not found when those with FLI > 60 were removed from the analyses (all p > 0.07 for VF, p > 0.6 for WLL).

3.4. Fatty-liver-index as a predictor for cognitive decline during 11 years

Baseline FLI group was associated with a greater decline in WLL during the 11-year follow-up (all Models p < 0.04). There was a difference between those with FLI > 60 and FLI 30–60 (all Models p < 0.03). When FLI > 60 was compared to FLI < 30, difference was seen only in Model 1 (p = 0.03). The results did not survive correction for multiple comparisons (Bonferroni-corrected $p >$ 0.06) (Table 4). Change in cognitive test scores is shown in Fig. 2.

The results are shown as adjusted means with 95 % confidence intervals for cognitive test score at baseline minus cognitive test score at follow-up. *P*-value indicates overall difference between groups, assessed with linear models. Tukey's HSD was used to analyze pairwise comparisons between groups. In model 1, adjustments were made for age, sex and education. Model 2 included adjustments for hypertension, DM, hypercholesterolemia and *APOE* ε4 carriership in addition to variables included in the model 1. Model 3 was further adjusted for BDI score, physical activity and smoking status. Additional adjustments were made separately for HOMA-IR and hs-CRP in Model 2. All models were additionally adjusted for baseline cognitive test scores. FLI, HOMA-IR, hs-CRP, and BDI scores were treated with natural logarithm to achieve a normal distribution. Abbreviations: β=estimate; SE=standard error; FLI=fatty liver index; BDI=Beck's depression inventory; hs-CRP=high-sensitivity C-reactive protein; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance; DM=diabetes mellitus. Bonferroni-corrected *P*-values (uncorrected *P*-value*3, not performed on *P*-value from ANOVA). N = 3143.

We also performed additional multivariate linear regression analyses where baseline FLI was treated as a continuous variable. However, no associations for continuous baseline FLI and change in cognitive test scores during the follow-up were found.

Standardized estimates were extracted for analyzing the effect of covariates of Model 2 on the change in cognitive performance during the follow-up (Table S4).

Adjusted means for baseline and follow-up cognitive scores with 95 % confidence intervals. Mean values were adjusted for age, sex and education. The *p* value represents difference between groups when examining the rate of change in cognition during the follow-up period, adjusted for age, sex and years of education.

3.5. Global cognitive score

Cross-sectionally, in Model 1 and 2, higher FLI group associated with worse global cognition (overall p < 0.04, FLI > 60 compared to FLI < 30 p=0.03). Longitudinally, in Model 1, FLI predicted global cognitive score (overall p=0.008, FLI > 60 compared to FLI < 30 p=0.005). In Model 2, the difference was not as strong but persisted (overall p=0.02, FLI > 60 compared to FLI < 30 p=0.02). FLI group did not predict change in global cognitive score (all p > 0.9).

3.6. Interactions and stratified analyses

Interactions between FLI and age, sex, *APOE* ε4 carriership, and DM were tested with multiple linear regression analysis. The significance of interactions was set to p=0.1.

'Age*FLI' interacted on WLL (p=0.003) and DWLR (p=0.01). No further interactions were found. The interactions were tested in Model 2.

In age-stratified analyses, age was divided into two categories: subjects aged 30–64 (n = 1936) and subjects older than 64 years (n = 1118). In both age groups, age was left as a continuous variable in the analysis. In the group with subjects aged 30–64 years, FLI did not predict WLL (p=0.06) and DWLR scores (p=0.2). Similarly, for participants aged over 64 years, FLI was not a predictor of WLL (p=0.07) and DWLR scores (p=0.3).

4. Discussion

These results show that longitudinally, MASLD, defined as FLI > 60, independently predicts poorer WLL after 11 years and greater decline from baseline to follow-up in WLL. Baseline MASLD also predicted poorer global cognition, measured by combining the tests of different cognitive domains into one z-score, at follow-up. Continuous and categorical baseline FLI was associated with poorer SRT and VF cross-sectionally and with weaker VF longitudinally, but these associations did not survive adjustments for metabolic, cardiovascular and inflammatory covariates. However, MASLD was associated with poorer global cognition cross-sectionally independently of metabolic risk factors. Altogether, these findings underline the deteriorating effect that MASLD might have on cognitive

Table 3
Adjusted means and 95 % confidence intervals of follow-up cognitive test scores according to baseline fatty liver index groups.

	FLI < 30, n = 2329	FLI 30–60, n = 503	FLI > 60, n = 311	*P*-value ANOVA	*P*-value Tukey's HSD when comparing FLI > 60 to FLI < 30	*P*-value Tukey's HSD when comparing FLI > 60 to FLI 30–60	Bonferroni-corrected *P*-value Tukey's HSD when comparing FLI > 60 to FLI < 30	Bonferroni-corrected *P*-value Tukey's HSD when comparing FLI > 60 to FLI 30–60
Model 1								
Verbal fluency	24.3 (24.0 to 24.6)	23.6 (23.0 to 24.2)	23.5 (22.7 to 24.2)	**0.03**	0.1	1.0	0.3	
Word-list learning	21.1 (21.0 to 21.3)	21.3 (21.0 to 21.6)	20.4 (20.0 to 20.8)	**0.001**	**0.002**	**0.002**	**0.005**	**0.005**
Delayed word-list recall	7.2 (7.2 to 7.3)	7.3 (7.1 to 7.4)	7.0 (6.8 to 7.2)	0.1				
Model 2								
Verbal fluency	23.7 (22.8 to 24.6)	23.2 (22.2 to 24.1)	23.0 (22.0 to 24.0)	0.1				
Word-list learning	20.6 (20.2 to 21.1)	20.8 (20.3 to 21.4)	19.9 (19.3 to 20.5)	**0.002**	**0.006**	**0.002**	**0.02**	**0.005**
Delayed word-list recall	7.1 (6.8 to 7.3)	7.1 (6.8 to 7.4)	6.9 (6.6 to 7.1)	0.2				
Model 3								
Verbal fluency	23.2 (22.2 to 24.2)	22.9 (21.8 to 24.0)	22.6 (21.4 to 23.7)	0.3				
Word-list learning	20.1 (19.5 to 20.6)	20.3 (19.7 to 20.9)	19.3 (18.7 to 19.9)	**0.002**	**0.01**	**0.002**	**0.03**	**0.005**
Delayed word-list recall	6.9 (6.6 to 7.1)	6.9 (6.7 to 7.2)	6.6 (6.3 to 7.0)	0.09				
Model 2+HOMA-IR								
Verbal fluency	23.9 (23.0 to 24.8)	23.6 (22.6 to 24.7)	23.7 (22.6 to 24.9)	0.8				
Word-list learning	20.7 (20.2 to 21.1)	20.9 (20.4 to 21.5)	20.0 (19.4 to 20.7)	**0.005**	**0.04**	**0.003**	0.1	**0.009**
Delayed word-list recall	7.1 (6.8 to 7.3)	7.1 (6.8 to 7.4)	6.9 (6.6 to 7.2)	0.2				
Model 2+hs-CRP								
Verbal fluency	23.7 (22.8 to 24.6)	23.2 (22.2 to 24.2)	23.1 (22.0 to 24.1)	0.2				
Word-list learning	20.6 (20.1 to 21.1)	20.8 (20.3 to 21.4)	20.0 (19.4 to 20.5)	**0.003**	**0.02**	**0.003**	**0.05**	**0.008**
Delayed word-list recall	7.1 (6.8 to 7.3)	7.1 (6.8 to 7.4)	6.8 (6.6 to 7.1)	0.2				

Participants that attended both the Health 2000 and Health 2011 surveys were included in these analyses (n = 3143). Pairwise comparisons with Tukey's HSD were used to analyze differences between groups. Values are weighted means (95 % confidence intervals). In model 1, adjustments were made for age, sex and education. Model 2 included adjustments for Model 1 + hypertension, DM, hypercholesterolemia and *APOE* ε4 carriership. Model 3 was further adjusted for BDI score, physical activity and smoking status. Additional adjustments were made separately for HOMA-IR and hs-CRP in Model 2. FLI, HOMA-IR, hs-CRP, and BDI scores were treated with natural logarithm to achieve a normal distribution. Abbreviations: β=estimate; APOE=apolipoprotein E; BDI=Beck's depression inventory; DM=diabetes mellitus; FLI=fatty liver index; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance; hs-CRP=high-sensitivity C-reactive protein; HSD=honest significance test. Bonferroni-corrected *P*-values (uncorrected *P*-value*3, not performed on *P*-value from ANOVA).

Table 4
Adjusted mean change with 95 % confidence intervals of cognitive test scores during the 11-year follow-up period.

	FLI < 30, n = 2329	FLI 30–60, n = 503	FLI > 60, n = 311	*P*-value ANOVA	*P*-value Tukey's HSD when comparing FLI > 60 to FLI < 30	*P*- value Tukey's HSD when comparing FLI > 60 to FLI 30–60	Bonferroni-corrected *P*-value Tukey's HSD when comparing FLI > 60 to FLI < 30	Bonferroni-corrected *P*- value Tukey's HSD when comparing FLI > 60 to FLI 30–60
Model 1								
Verbal fluency	-0.8 (-1.1 to -0.6)	-1.1 (-1.6 to -0.6)	-1.0 (-1.6 to -0.4)	0.5				
Word-list learning	-0.5 (-0.7 to -0.4)	-0.4 (-0.7 to -0.1)	-1.0 (-1.4 to -0.7)	**0.01**	**0.03**	**0.01**	0.09	**0.04**
Delayed word-list recall	-0.2 (-0.4 to -0.2)	-0.2 (-0.3 to -0.07)	-0.3 (-0.5 to -0.2)	0.4				
Model 2								
Verbal fluency	-1.4 (-2.1 to -0.6)	-1.6 (-2.4 to -0.8)	-1.4 (-2.2 to -0.5)	0.8				
Word-list learning	-0.9 (-1.3 to -0.5)	-0.7 (-1.2 to -0.3)	-1.4 (-1.9 to -0.9)	**0.03**	0.09	**0.02**	0.3	0.06
Delayed word-list recall	-0.3 (-0.5 to -0.09)	-0.3 (-0.5 to -0.04)	-0.4 (-0.6 to -0.2)	0.5				
Model 3								
Verbal fluency	-1.7 (-2.5 to -0.9)	-1.8 (-2.7 to -0.9)	-1.7 (-2.7 to -0.8)	0.9				
Word-list learning	-1.3 (-1.8 to -0.8)	-1.1 (-1.6 to -0.5)	-1.7 (-2.3 to -1.2)	**0.03**	0.1	**0.03**	0.1	0.08
Delayed word-list recall	-0.4 (-0.6 to -0.2)	-0.4 (-0.6 to -0.1)	-0.5 (-0.8 to -0.3)	0.3				
Model 2+HOMA-IR								
Verbal fluency	-1.3 (-2.0 to -0.6)	-1.3 (-2.1 to -0.4)	-1.0 (-1.9 to -0.04)	0.7				
Word-list learning	-0.9 (-1.3 to -0.5)	-0.7 (-1.2 to -0.2)	-1.3 (-1.8 to -0.7)	**0.04**	0.2	**0.03**	0.7	0.08
Delayed word-list recall	-0.3 (-0.5 to -0.08)	-0.2 (-0.5 to -0.005)	-0.4 (-0.6 to -0.1)	0.6				
Model 2+hs-CRP								
Verbal fluency	-1.4 (-2.1 to -0.7)	-1.5 (-2.3 to -0.7)	-1.3 (-2.2 to -0.5)	0.9				
Word-list learning	-0.9 (-1.4 to -0.5)	-0.7 (-1.2 to -0.3)	-1.3 (-1.8 to -0.8)	**0.04**	0.2	**0.03**	0.5	0.08
Delayed word-list recall	-0.3 (-0.5 to -0.09)	-0.3 (-0.5 to -0.04)	-0.4 (-0.6 to -0.1)	0.6				

The results are shown as adjusted means with 95 % confidence intervals for cognitive test score at baseline minus cognitive test score at follow-up. *P*-value indicates overall difference between groups, assessed with linear models. Tukey's HSD was used to analyze pairwise comparisons between groups. In model 1, adjustments were made for age, sex and education. Model 2 included adjustments for hypertension, DM, hypercholesterolemia and *APOE* ε4 carriership in addition to variables included in the model 1. Model 3 was further adjusted for BDI score, physical activity and smoking status. Additional adjustments were made separately for HOMA-IR and hs-CRP in Model 2. All models were additionally adjusted for baseline cognitive test scores. FLI, HOMA-IR, hs-CRP, and BDI scores were treated with natural logarithm to achieve a normal distribution. Abbreviations: β=estimate; APOE=apolipoprotein E; BDI=Beck's depression inventory; DM=diabetes mellitus; FLI=fatty liver index; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance; hs-CRP=high-sensitivity C-reactive protein; HSD=honest significance test. Bonferroni-corrected *P*-values (uncorrected *P*-value*3, not performed on *P*-value from ANOVA). N = 3143

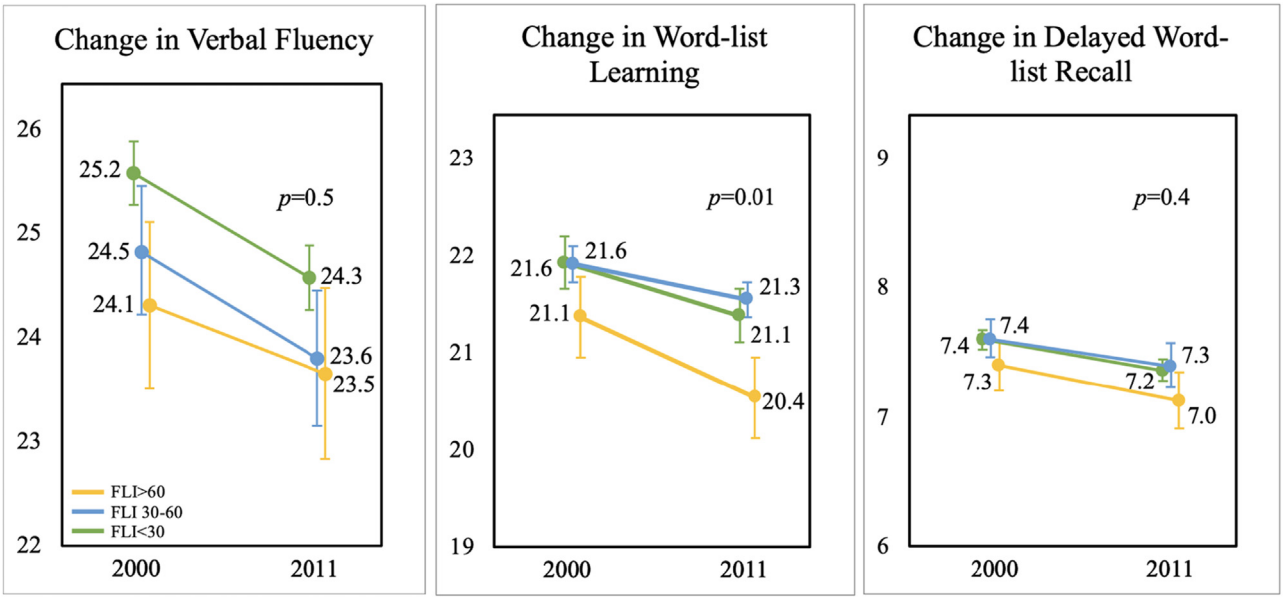

Fig. 2. Change in cognitive tests over the 11-year follow-up in different fatty liver index groups. Adjusted means for baseline and follow-up cognitive scores with 95 % confidence intervals. Mean values were adjusted for age, sex and education. The *p* value represents difference between groups when examining the rate of change in cognition during the follow-up period, adjusted for age, sex and years of education. Abbreviations: FLI=fatty liver index.

functions, as is shown by poorer WLL during follow-up among those with MASLD. No longitudinal associations between continuous FLI and cognitive performance were found, which suggests that the current cut-off for FLI to define MASLD seems to apply for predicting an increased risk for decline in cognition. Additionally, the results highlight the importance of metabolic aspect of MASLD since adjusting for metabolic and cardiovascular risk factors decreased the significance of FLI as a predictor of cognitive performance.

There are a number of studies that have evaluated the association between MASLD and cognitive function cross-sectionally [2–4,6,12,14–17]. Consistently, MASLD has been shown to associate with poorer executive function in middle-aged individuals [14,15]. These associations seem to be more prominent in individuals with low-grade inflammation [18]. In line with the previous studies, we have shown that MASLD associates with slower processing speed (SRT) and with poorer VF, which is considered to reflect executive functions.

Previously, only a few studies have explored the associations between MASLD and cognition longitudinally. REGARDS, a prospective cohort study of 587 subjects aged 45 or over at baseline, found that MASLD has a significant association with decreased cognitive function after a follow-up of 3.4 years before adjusting for sociodemographic and cardiovascular risk factors, and that MASLD is a more significant risk factor for cognitive dysfunction in middle-aged individuals than in the older population [13]. A large, nationwide register-based Korean study showed that MASLD was associated with an increased risk for dementia during a follow-up of 9.5 years [5]. Our study extends these previous studies by providing cognitive testing at both baseline and at follow-up allowing us to evaluate the change in cognitive performance over time and by extending the follow-up to 11 years.

It has previously been suggested that MASLD could cause cognitive decline *via* its metabolic and cardiovascular components. In a population-based CARDIA study, 505 middle-aged subjects were examined to evaluate whether MASLD associates with decreased brain health measured by magnetic resonance imaging. This study found cross-sectional associations between MASLD and decreases in global brain volume and cerebral blood flow before adjusting for visceral adiposity and cardiovascular factors in middle-aged adults [11]. Aligned with this, cross-sectional analyses using population-based NHANES data concluded that over 60-year-old subjects (n = 1102) with T2DM and/or MASLD perform more poorly in VF and digit symbol substitution tests than those without these conditions, highlighting the effect of IR [17]. The population with both T2DM and MASLD showed worse performance in the digit substitution test compared to those with only T2DM, indicating slower processing speed and executive function [17]. This, again, underlines the importance of the metabolic component of MASLD in the deterioration of cognitive function. In line with the previous results, our study implies that, cross-sectionally, those with MASLD tend to perform more slowly in the SRT test that reflects processing speed.

To explain the previous associations and their decreasing significance after adjusting for metabolic and cardiovascular risk factors, IR has been suggested to be a possible bridging component. Metabolic and cardiovascular diseases are often characterized by IR which, in turn, is characterized by decreased sensitivity of tissues to insulin and sustained hyperglycemia. IR closely associates with MASLD, although it is controversial whether steatosis of liver predisposes to IR or vice versa [29]. Nevertheless, IR has been shown to associate with decreased VF [27,28] and a steeper decline in episodic memory [30] in the Finnish adult population. IR has also been suggested to be a risk factor for AD [31]. Thus, MASLD could associate with decreased cognition *via* inducing IR.

Current view of the pathogenesis of MASLD involves systemic low-grade inflammation as a contributing factor. This is evident especially when considering inflammation of visceral adipose tissue in the process of accumulation of fat in the liver [32]. Additionally, increase in inflammation in the liver is pivotal in the progression of MASLD. Sided with this, inflammation is also present in conditions causing decreases in cognitive function such as Alzheimer's disease. [33,34]. Thus, it is of consideration if MASLD contributes additively to the level of peripheral inflammation.

MASLD has also been suggested to be associated with poorer cognitive function independently of the risk factors considered before. In our study, MASLD predicted poorer performance and a greater decline in WLL independent of metabolic risk factors. In

fact, it has been shown that histological severity of MASLD associates with presence of white matter lesions [35] which could cause deficits in working memory, thus worsening the performance on the WLL test. In accordance, a cross-sectional study with NHANES III data found that among 4472 middle-aged subjects, MASLD was associated with worse learning, recall and concentration functions independent of cardiovascular risk factors [3]. Furthermore, a study examining association between MASLD and cognitive function among middle-aged adults from the Framingham survey (n = 1287) found that those with high risk of advanced MASLD independently exhibit poorer performance in executive function and abstract reasoning [2].

Strengths of this study were the large, representative sample of the Finnish adult population and the large amount of information about cardiovascular, metabolic and cognitive risk factors. Additionally, the 11-year follow-up period and repeated cognitive measurements were of importance in studying the effect MASLD has over time. However, this study also had limitations. Not all associations between MASLD and cognition survived a strict Bonferroni correction for the number of cognitive tests that were analyzed. However, these cognitive tests represent distinct cognitive domains which are thought to represent the function of different brain regions (frontotemporal regions for processing speed (SRT), prefrontal regions for executive functions (VCRT, VF), frontotemporal regions for working memory (WLL), and finally, medial temporal regions for episodic memory (DWLR) [36,37]. Therefore, it can be argued that the cognitive tests that were performed were independent measures different cognitive domains, and that the results can be interpreted without multiple comparison corrections. A more accurate method for determining the prevalence of MASLD could have provided us with more detailed results. Furthermore, different values of FLI have been used in different studies, and although FLI $>$ 60 adequately predicts MASLD, it still predicts fatty liver with a certain degree of uncertainty. Also, the number of participants with FLI $>$ 60 in this study population was relatively low. The cognitive tests used are not very sensitive in middle-aged individuals. Lastly, we did not have follow-up results for SRT for which strongest associations with MASLD were found in our cross-sectional analysis.

In conclusion, we have shown MASLD to be independently associated with poorer WLL and a greater decline in WLL longitudinally. MASLD also predicted worse global cognition longitudinally. Our study implies that cross-sectionally, MASLD associates with global cognitive function independently, and with poorer VF and SRT *via* its cardiovascular and/or metabolic component. Since people with MASLD are often asymptomatic until the disease progresses to a more severe stage, interventions need to be made earlier. Further research is needed to examine the effects and mechanisms that MASLD may have on cognition to prevent cognitive decline in this at-risk population.

Conflicts of interest

No conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.01.197.

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