

# Association of fatty liver disease with mortality outcomes in an Eastern Finland male cohort

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## ABSTRACT

**Objective** Fatty liver disease (FLD) has been associated with extrahepatic morbidity outcomes. However, reports on the association of FLD, assessed using fatty liver index (FLI), with mortality outcomes have been inconsistent. Our objective was to examine the effect of metabolic factors (blood pressure, insulin, fasting glucose, lipoproteins) on the associations of FLI with mortality outcomes among middle-aged men.

**Study design** Prospective cohort study.

**Methods** Our subjects were 1893 men at baseline from 1984 to 1989 in the Kuopio Ischaemic Heart Disease Risk Factor Study cohort. Multivariable Cox regression models were used to analyse the association of baseline FLI, with the HRs for all-cause, disease, cardiovascular, non-cardiovascular and cancer mortality outcomes.

**Results** The mean FLI in the FLI categories were 16.2 in the low and reference category (FLI<30), 43.4 in the intermediate FLI category (FLI=30–<60) and 77.5 in the high FLI (FLD) category (FLI≥60). Over an average follow-up of 20 years, 848 disease deaths were recorded through Finnish national cause of death register. In models adjusted for constitutional, lifestyle and inflammatory factors, for the high (FLI≥60) vs low (FLI<30) FLI category, the HRs (95% CI) for mortality outcomes were 1.50 (1.26–1.78) for all-cause mortality; 1.56 (1.31–2.86) for disease mortality; 1.51 (1.18–1.94) for cardiovascular disease (CVD) mortality; 1.42 (1.12–1.80) for non-CVD mortality and 1.45 (1.02–2.07) for cancer mortality. With further adjustment for metabolic factors, the HRs were 1.25 (1.01–1.53) for all-cause mortality; 1.26 (1.02–1.56) for disease mortality; 1.06 (0.78–1.43) for CVD mortality; 1.46 (1.09–1.94) for non-CVD mortality and 1.49 (0.97–2.29) for cancer mortality.

**Conclusion** High FLI (FLD) is associated with increased risks of mortality outcomes. The FLI-CVD mortality association can be largely explained by metabolic factors. Persons with FLD should be monitored for metabolic deterioration and extrahepatic morbidity to improve their prognoses.

## INTRODUCTION

Fatty liver disease (FLD) is an epidemic with increasing proportions and is now the most common cause of chronic liver disease in Western countries. It has been estimated that 25% of the global population have

## Summary box

### What is already known about this subject?

► Fatty liver disease (FLD), an epidemic of increasing proportions, is associated with extrahepatic morbidity.

### What are the new findings?

- FLD is associated with increased risk of all-cause mortality and disease mortality.
- It is associated with increased risk of cardiovascular disease (CVD) mortality, non-CVD mortality and cancer mortality.
- However, the FLD-CVD mortality association can be largely explained by metabolic factors.

### How might it impact on clinical practice in the foreseeable future?

- Early detection of FLD can be highly beneficial.
- Persons with FLD should be monitored for metabolic deterioration and extrahepatic morbidity to improve their prognoses.

non-alcoholic fatty liver disease (NAFLD), with highest prevalence in the Middle East and South America and lowest prevalence in Africa.<sup>1,2</sup> Of greater concern is the association of fatty liver with extrahepatic diseases, such as type 2 diabetes, cardiovascular diseases (CVDs) and chronic kidney disease.<sup>3–5</sup> It is therefore logical to speculate association of FLD with increased mortality risk consequent on the association of these diseases with increased mortality globally.<sup>6</sup>

However, in relation to this speculation, reports on the association of FLD with mortality have been conflicting. Although Stepanova *et al*<sup>7</sup> reported that ultrasound diagnosed NAFLD was associated with increased risk of CVD, they found no association with cardiovascular mortality. Similarly, Lazo *et al*<sup>8</sup> found no association between ultrasound diagnosed NAFLD and increased risk of all-cause, cardiovascular or cancer mortality outcomes. In addition, reports from studies with ultrasound diagnosed FLD



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suggest increased scores of algorithm-based assessed markers of fibrosis are associated with different mortality outcomes among NAFLD subjects.<sup>9–11</sup> However, reports from studies using algorithm-based surrogate of fatty liver suggest disparate associations.<sup>12–15</sup> Some of these reports suggest that the association of FLD with mortality outcomes may be connected with metabolic factors.<sup>12–15</sup> Indeed, the epidemiology of FLD has been closely linked with the epidemiology of metabolic diseases and the increasing incidence of FLD has been accompanied by increasing incidence of metabolic diseases.<sup>16</sup> Moreover, FLD is known to be associated with insulin resistance and other features of metabolic syndrome.<sup>17–18</sup> On the other hand, emerging evidence suggest that cardiovascular and cancer mortality outcomes are closely linked with metabolic factors.<sup>19–20</sup> Hence, metabolic factors may play a role in the association of FLD with mortality outcomes.

Using fatty liver index (FLI), a validated surrogate of FLD,<sup>21–23</sup> the aim of this study is to examine the relationship between FLD and mortality outcomes and to document the effect of metabolic factors on the observed association of FLD with mortality outcomes. The FLI has been found to have a high accuracy rate in detecting fatty liver (0.84; 95% CI 0.81 to 0.87) and can be easily applied in epidemiological studies.<sup>21</sup> Our hypothesis is that the association of high FLI (FLD) with the different mortality outcomes is influenced differently by metabolic factors. The extrahepatic mortality outcomes of interest in this study are all-cause mortality, CVD mortality, non-cardiovascular mortality and cancer mortality.

## METHODS

### Study population

Our study subjects were participants in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD). The KIHD is a prospective population-based study designed to investigate risk factors for CVDs and related outcomes, in middle-aged and ageing men, from Eastern Finland. The original study population comprised of 2682 men who were aged 42, 48, 54 and 60 years, from the general male population in Eastern Finland. The men were age-stratified, with ages 42, 48, 54 or 60 years when they were enrolled at the baseline examinations between March 1984 and December 1989. The study was approved by the Research Ethics Committee of the University of Kuopio, in Eastern Finland, and all subjects gave written informed consent.

### Study design

In this prospective cohort study, we examine the effect of metabolic factors (blood pressure, insulin, fasting glucose, lipoproteins) on the prospective associations of FLD (assessed using FLI), with mortality outcomes among the KIHD participants.

### Data collection

Data were collected through self-administered questionnaires, interviews, physical examinations and various

blood tests to determine physiological and biochemical parameters.

The self-administered questionnaire was used to elicit data on medical history, medication history, family history of metabolic and CVDs as well as lifestyle history including physical activity, smoking habit, alcohol consumption and diet.

The interviews were to corroborate data on medical history and lifestyle.<sup>24</sup> The physical examinations, including anthropometric measurements and indices, vital signs and physiological measurements were measured following standard protocol. Waist circumference was calculated as the mean of waist circumference taken at maximal inspiration and that taken at maximal expiration. Body mass index (BMI) was computed as the ratio of weight in kg to the square of height in metres ( $\text{kg}/\text{m}^2$ ). Blood pressure was taken as the mean of three measurements in supine position, two in sitting position with 5 min intervals and one in standing position.<sup>25</sup> Dietary intake was assessed at time of blood sampling with an instructed and interview checked 4 day diet record by household measures.<sup>26</sup>

### Specimen collection, laboratory analyses and laboratory data

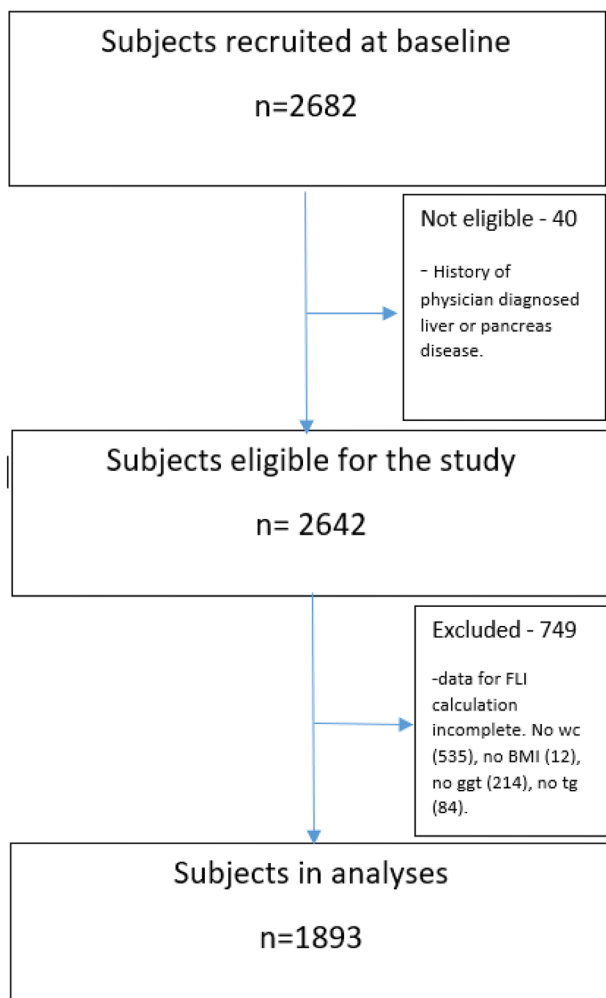
For the physiological, biochemical, biomarker and cellular blood tests, blood samples were collected between 08:00 and 10:00 hours after 3 days of abstinence from alcohol ingestion and 12 hours abstinence from smoking and eating.<sup>27</sup> Data on complete blood count, serum electrolytes, insulin, HOMA1-IR insulin resistance, fasting glucose,<sup>28</sup> lipoprotein fractions (including total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, serum triglycerides),<sup>29</sup> liver function proteins including albumin, gamma-glutamyl transferase (GGT), fibrinogen<sup>27</sup> and other serum proteins like ferritin and biomarkers like C reactive protein<sup>30</sup> were each determined.

### Included and excluded subjects

We included men enrolled at the baseline of the KIHD. The initial number of subjects at baseline was 2682. Of these, we excluded 40 subjects with self-reported history of physician diagnosed liver or pancreas disease. Of the remaining 2642 men, 749 had missing values in one or more FLI component variables and were also excluded. Therefore, 1893 men who had complete data for FLI calculation were studied (figure 1).

### Determination of baseline fatty liver

We calculated FLI, a surrogate marker of fatty liver, from the algorithm developed by Bedogni *et al.*<sup>21</sup> The algorithm was developed through bootstrapped stepwise logistic regression analysis of 13 variables related to fatty liver to yield four variables namely, BMI, waist circumference, triglycerides and GGT.<sup>21</sup> The algorithm is expressed as follows:



**Figure 1** Flowchart depicting the selection of study participants. BMI, body mass index; FLI, fatty liver index; ggt,  $\gamma$ -glutamyl transferase, tg, triglycerides; wc, waist circumference.

$$FLI = \frac{e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \ln(\text{ggt}) + 0.053 \times \text{waist circumference} - 15.745}}{1 + e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \ln(\text{ggt}) + 0.053 \times \text{waist circumference} - 15.745}} \times 100$$

where triglycerides are in mg/dL, ggt is  $\gamma$ -glutamyl transferase in U/L, waist circumference is in cm and BMI is body mass index in  $\text{kg}/\text{m}^2$ . FLI categorisation was also done in accordance with Bedogni *et al*, as low FLI ( $<30$ ), intermediate FLI ( $30\text{--}60$ ) and moderate-high FLI ( $>60$ ), indicating no fatty liver, indeterminate and fatty liver, respectively.

### Outcomes definitions

Deaths were determined by linkage to the Finnish national cause of death register using the Finnish personal identification code (social security number). The deaths were coded according to the Tenth International Classification of Disease (ICD) codes. There were no losses to follow-up. We included all deaths that occurred from the study entry to 31 December 2012 in our analysis. Disease deaths included all deaths coded with ICD 10

codes between A00 and R99 and excluded deaths due to accidents or suicides (ICD codes S00-T98). Cardiovascular deaths were deaths due to ICD 10 codes I00-I99. Non-cardiovascular death was defined as disease death excluding those due to ICD 10 codes I00-I99. Cancer death included deaths due to ICD 10 codes C00-C97.

### Statistical methods

All statistical analyses were performed using SPSS software V.25.0 for Windows (IBM, Chicago, Illinois, USA). All eligible subjects had complete data for FLI calculation. Descriptive statistical analyses (mean $\pm$ SD or percentages) were performed to summarise the baseline characteristics of the participants according to their baseline FLI categories. Comparisons between FLI categories were performed using Jonckheere trend test for continuous variables and  $\chi^2$  test for categorical variables. We performed missing value analysis to determine the variables with missing values and to estimate the degree of missingness for each variable. We used a regression based multiple imputation method (40 iterations) to make up for missing values in covariates, according to guideline by Cheema.<sup>31</sup>

We confirmed the assumptions of proportionality of hazards for each mortality outcome with log-rank test by FLI category at baseline. Constitutional (age, family history of diabetes, family history of CVD), lifestyle (smoking status, alcohol consumption, physical activity and fruit, berry and vegetable consumption), inflammatory factor (C reactive protein, fibrinogen, leucocytes and thrombocytes) and metabolic factor (hypertension, insulin, fasting glucose, LDL and HDL) variables were used in multivariable adjusted Cox proportional hazards analysis in models with progressive adjustments, to analyse the association of baseline FLI, with the HR for all-cause, cardiovascular, non-cardiovascular and cancer mortality outcomes. The models were designed as follows: Model 1: FLI category, examination date, constitutional factors and lifestyle factors. Model 2: Model 1 plus inflammatory factors and Model 3: Model 2 plus metabolic factors. In the analyses of association with cardiovascular mortality and cancer mortality, history of CVD and history of cancer were included in Model 1 of the respective analyses. Two-sided  $p < 0.05$  was considered statistically significant.

In sensitivity analyses, we excluded individuals with a high weekly alcohol consumption of  $\geq 168$  g based on previous publication<sup>32</sup> before analysing the association of FLI with the mortality outcomes in multivariable adjusted Cox proportional hazards as explained above.

## RESULTS

### Characteristics of the study population

The baseline characteristics of the study population are shown in table 1, according to FLI categories. Compared with subjects in the lowest FLI category, subjects in the high FLI category consumed less fruits, berries and

**Table 1** Baseline characteristics of 1893 men according to FLI categories

Characteristic (No.)	FLI<30 Mean (SD) or n (%) N=847	FLI=30–<60 Mean (SD) or n (%) N=571	FLI≥60 Mean (SD) or n (%) N=475	P trend*
FLI (n=1893)	16.2 (7.7) (N=847)	43.4 (8.2) (N=571)	77.51 (11.2) (N=475)	<0.001
Constitutional factors				
Age in years (n=1893)	52.6 (5.6)	53.5 (5.5)	52.8 (5.6)	0.113
Family history of diabetes	217 (25.6%)	156 (27.3%)	144 (30.3%)	0.074
Family history of CVD	675 (79.7%)	474 (83.0%)	397 (83.6%)	0.053
Lifestyle factors				
Smoking (pack years)	8.66 (17.01)	7.78 (15.94)	6.91 (14.20)	0.24
Alcohol consumption category (g/week)	55 (88)	77 (116)	115 (163)	<0.001
Physical activity (Energy exp.) (kcal/day)	136.1 (156.3)	146.8 (173.6)	135.3 (199.6)	0.33
Fruit, berry and vegetable consumption (g/day)	165.8 (148.1)	163.9 (142.0)	145.4 (141.9)	0.001
Anthropometrics and physiological measurements				
Mean waist circumference (cm)	83.9 (6.1)	92.70 (5.24)	102.4 (8.6)	<0.001
BMI (kg/m <sup>2</sup> )	24.4 (2.0)	27.3 (1.93)	30.9 (3.3)	<0.001
Systolic blood pressure	128.7 (16.1)	133.7 (15.8)	139.8 (16.6)	<0.001
Diastolic blood pressure	84.7 (9.9)	89.3 (9.8)	92.8 (10.2)	<0.001
Hypertension	267 (31.5%)	289 (50.6%)	314 (66.1%)	<0.001
Biomarkers				
Fasting glucose (mmol/L)	4.5 (0.7)	4.7 (0.7)	5.3 (1.9)	<0.001
HOMA1-IR insulin resistance	1.91 (0.93)	2.70 (1.27)	4.82 (3.93)	<0.001
Serum Insulin mU/L	8.3 (3.0)	11.3 (4.5)	17.8 (10.7)	<0.001
Total cholesterol (mmol/L)	5.71 (1.07)	5.92 (1.01)	6.02 (1.08)	<0.001
HDL cholesterol (mmol/L)	1.38 (0.32)	1.25 (0.27)	1.19 (0.27)	<0.001
LDL cholesterol (mmol/L)	3.92 (1.01)	4.94 (0.96)	3.96 (0.95)	0.04
Serum triglycerides (mmol/L)	0.93 (0.40)	1.36 (0.62)	1.98 (1.09)	<0.001
Serum triglyceride mg/dL	82.7 (35.6)	120.3 (55.0)	175.5 (96.7)	<0.001
Serum gamma-glutamyl transferase (U/L)	18 (11)	28 (20)	53 (52)	<0.001
Serum fibrinogen (g/L)	2.92 (0.58)	3.06 (0.57)	3.14 (0.58)	<0.001
C reactive protein (m/L)	1.88 (4.45)	2.69 (4.74)	3.31 (4.32)	<0.001
Serum ferritin (µg/L)	127 (91)	174 (178)	262 (194)	<0.001
Leucocyte count ×10 <sup>9</sup> /L	5.4 (1.6)	5.7 (1.5)	6.0 (1.7)	<0.001
Thrombocyte count ×10 <sup>9</sup> /L	5.2 (1.5)	5.6 (1.4)	5.7 (1.6)	<0.001
Baseline morbidity and drug history				
History of CVD	275	197	216	<0.001
History of cancer	10	14	10	0.129
Drug for high cholesterol	7	2	6	0.623
Drug for hypertension	117	134	176	<0.001

\*Jonckheere trend test for continuous variable.  $\chi^2$  linear-by-linear association for categorical variables. BMI, body mass index; CVD, cardiovascular disease; FLI, fatty liver index.

vegetables and were more likely to be heavy consumers of alcohol. Their mean waist circumference and mean BMI and, systolic and diastolic blood pressures, were higher. They had higher fasting insulin and blood glucose levels and were also more likely to be insulin resistant, with higher triglyceride and GGT levels.

### FLI and all-cause mortality

During an average follow-up of 20 years, 848 disease related deaths were registered. In the first model, compared with the low FLI category (no fatty liver), we observed approximately 67% increase in mortality risk in the high FLI category (table 2). The association was



**Table 2** HRs and CIs of all-cause, cardiovascular, non-cardiovascular and cancer mortality by FLI categories

Outcome/FLI category		Model 1 HRs (95% CI)	Model 2 HRs (95% CI)	Model 3 HRs (95% CI)
<b>All-cause mortality</b>				
≤30 (Ref.)	330	1.00	1.00	1.00
30–<60	254	1.11 (0.94 to 1.30)	1.03 (0.87 to 1.22)	0.98 (0.82 to 1.17)
≥60	264	1.67 (1.42 to 1.98)	1.50 (1.26 to 1.78)	1.25 (1.01 to 1.53)*
P trend		<0.001	<0.001	0.058
<b>Disease mortality</b>				
≤30 (Ref.)	301	1.00	1.00	1.00
30–<60	235	1.12 (0.94 to 1.33)	1.04 (0.87 to 1.24)	0.98 (0.81 to 1.17)
≥60	246	1.74 (1.46 to 2.08)	1.56 (1.31 to 1.86)	1.26 (1.02 to 1.56)
P trend		<0.001	<0.001	0.056
<b>CVD mortality</b>				
≤30 (Ref.)	148	1.00	1.00	1.00
30–<60	119	1.14 (0.89 to 1.46)	1.03 (0.80 to 1.32)	0.93 (0.72 to 1.20)
≥60	132	1.71 (1.34 to 2.19)	1.51 (1.18 to 1.94)	1.06 (0.78 to 1.43)†
P trend		<0.001	0.002	0.78
<b>Non-CVD mortality</b>				
≤30 (Ref.)	182	1.00	1.00	1.00
30–<60	135	1.07 (0.85 to 1.34)	1.03 (0.82 to 1.29)	1.07 (0.84 to 1.36)
≥60	132	1.53 (1.21 to 1.93)	1.42 (1.12 to 1.80)	1.46 (1.09 to 1.94)‡
P trend		0.001	0.007	0.016
<b>Cancer mortality</b>				
≤30 (Ref.)	83	1.00	1.00	1.00
30–<60	69	1.20 (0.87 to 1.66)	1.17 (0.84 to 1.62)	1.17 (0.83 to 1.66)
≥60	57	1.54 (1.09 to 2.18)	1.45 (1.02 to 2.07)	1.49 (0.97 to 2.29)§
P trend		0.016	0.042	0.076

Model 1: FLI category, examination date, age, family history of diabetes, family history of cardiovascular disease, smoking status, alcohol consumption, physical activity, fruit, berry & berry consumption (and CVD history for CVD mortality) (and cancer history for cancer mortality).  
Model 2: Model 1 plus C reactive protein, fibrinogen, leucocytes and thrombocytes.

Model 3: Model 2 plus systolic blood pressure, diastolic blood pressure, insulin, fasting glucose, LDL, HDL.

\*All-cause mortality: Other independent predictors were age, smoking packyears, alcohol consumption, fibrinogen, leucocyte count, systolic blood pressure and glucose.

†CVD mortality: Other independent predictors were age, smoking packyears, alcohol consumption, fibrinogen, leucocyte count, systolic blood pressure and glucose.

‡Non-CVD mortality: Other independent predictors were age, smoking packyears, alcohol consumption, leucocyte count and glucose.

§Cancer mortality: Other independent predictors were age, smoking packyears and thrombocyte count.

¶Disease mortality: Other independent predictors were age, smoking packyears, alcohol consumption, fibrinogen, leucocyte count, systolic blood pressure and glucose.

\*\*Statistically significant at  $p \leq 0.05$ .

CVD, cardiovascular disease; FLI, fatty liver index; Ref, reference.

attenuated with further adjustment, and in the model 3, there was 25% increase in risk (but a 25% further drop in HR from the HR in the previous model).

### FLI and disease mortality

During an average follow-up of 20 years, 782 disease related deaths were registered. In the first model, compared with the low FLI category (no fatty liver), we observed approximately 74% increase in mortality risk in the high FLI category (table 2). The association was attenuated with further adjustment, and in the model 3,

there was 26% increase in risk (but a 30% further drop in HR from the HR in the previous model).

### FLI and cardiovascular disease mortality

During the 20-year observation period, 399 deaths were attributed to CVD. In the first model, we observed 71% increase in HR of CVD mortality (HR=1.71 (1.34–2.19), in the high FLI category, when compared with the low FLI category. The association was attenuated but maintained in model 2 (table 2). However, the association was extenuated in our most comprehensively adjusted



model, with a 45% further drop in HR, when we added metabolic factors (hypertension, insulin, fasting glucose, LDL, HDL).

### FLI and non-cardiovascular disease mortality

During the follow-up, 449 deaths were attributed to non-CVD-related disease. In model 1, we observed 53% increase in HR of non-CVD mortality (HR=1.52 (1.20–1.93) for the high FLI category, when compared with the low FLI category (table 2). The association was attenuated, but maintained in model 2 and in model 3 when we added metabolic factors (hypertension, insulin, fasting glucose, LDL, HDL), there was a 4% increase in HR in model 3 compared with model 2.

### FLI and cancer mortality

During the follow-up, 209 deaths were attributed to a malignancy. In model 1, we observed 54% increase in HR of cancer mortality (HR=1.54 (1.09–2.19), in the high FLI category, when compared with the low FLI category (table 2). The association was attenuated but maintained with further adjustment in model 2. However, in model 3 when we added metabolic factors (hypertension, insulin, fasting glucose, LDL, HDL), the association was borderline, with a 4% increase in HR.

### Sensitivity analyses

After excluding heavy alcohol consumers (see table 3). The results were similar to what we obtained in the analyses with whole sample. In model 3, when we added metabolic factors, the greatest drop in HR was in HR for CVD mortality (approximately 50% drop in HR). Outcomes incorporating CVD mortality had greater drops in HR. However, there were a few notable differences. For all-cause mortality and disease mortality, the association of high FLI with the mortality outcome did not reach statistical significance in our most extensively adjusted model, when we added the metabolic factors, even though the association was strongly significant in earlier models. Also for cancer mortality, the association of high FLI with cancer mortality did not reach statistical significance in the extensively adjusted models when we added markers of inflammation in addition to constitutional factors and lifestyle factors and furthermore when we added metabolic factors.

## DISCUSSION

In this study, we assessed the relationship between FLD and mortality outcomes and observed the effect of metabolic factors on the association of FLD with mortality outcomes in middle-aged and older men enrolled in the KIHHD study. We found that high FLI category, which represents FLD, was associated with increased risk of all-cause, disease, cardiovascular, non-cardiovascular and cancer mortality. However, the association with CVD mortality was remarkably attenuated by metabolic factors, including systolic blood pressure, diastolic blood pressure, insulin, fasting glucose, LDL and HDL. The

associations with all-cause mortality and disease mortality (outcomes that incorporated CVD mortality) were also markedly attenuated by metabolic factors. Our findings suggest both that subjects with the FLD carry an increased risk for mortality and that the association of FLD with CVD mortality is almost fully explained by associated metabolic factors. They also suggest that the association of fatty liver with extrahepatic morbidity may have significant impact on overall mortality outcomes.

The few studies that have explored the association of FLI with mortality outcomes have given inconsistent reports. While the first two, Calori *et al*<sup>15</sup> and Lerchbaum *et al*<sup>13</sup> reported a positive association, the latest two, Otgonsuren *et al*<sup>14</sup> and Onat *et al*<sup>12</sup> had contrary reports. Lerchbaum *et al*, who studied a series of patients referred for coronary angiography, reported high FLI levels to be independently associated with increased all-cause, cardiovascular and non-cardiovascular mortality.<sup>13</sup>

However, we noted that Calori *et al* stated that the association they found between FLI and mortality events appeared to be tightly connected with the risk conferred by insulin-resistant state.<sup>15</sup> Interestingly also, Onat *et al* thought that although they found no association, high FLI could likely predict mortality in a population of prediabetic patients.<sup>12</sup> Factors that constitute the prediabetic state include insulin resistance, elevated fasting blood glucose, hypertension, elevated LDL cholesterol and low HDL cholesterol. These factors are known to be risk for type 2 diabetes and CVD.<sup>33</sup> Our study explicates the contradiction in previous studies by observing the association of FLD with mortality outcomes in a general population and documenting the effect of these metabolic factors on the association.

Our finding of the association of high FLI with all-cause, CVD, non-CVD and cancer mortality is consistent with the findings by Calori *et al*.<sup>15</sup> Because we have analysed with the three FLI categories, our study is not directly comparable with Lerchbaum *et al*,<sup>13</sup> who analysed with FLI quartiles or with Otgonsuren *et al*,<sup>14</sup> who analysed using log-transformed FLI.

In our main analyses, we did not exclude subjects in the heavy alcohol consumption category, but we controlled for alcohol consumption when we included the lifestyle risk factors in the models. However, we reanalysed the data, after excluding subjects with heavy alcohol consumption. We found that the results were generally similar to those obtained from the analyses without exclusion of high alcohol consumption category.

Presently, the mechanisms underlying the observed association of FLD with all-cause mortality are unclear. Studies have shown that the leading causes of death in patients with FLD are CVD, cancer and liver disease.<sup>34</sup> Indeed, in the general population, metabolic health can mediate mortality,<sup>35</sup> hence the connection of the association of FLI and CVD mortality with metabolic factors. Furthermore, FLD is a metabolic condition in which progression is associated with deterioration in metabolic health and is marked by increase in abnormalities in

**Table 3** HRs and CIs of all-cause, cardiovascular, non-cardiovascular and cancer mortality by FLI categories—after excluding men with high alcohol consumption

Outcome/FLI category		Model 1 HRs (95% CI)	Model 2 HRs (95% CI)	Model 3 HRs (95% CI)
<b>All-cause mortality</b>				
≤30 (Ref.)	295	1.00	1.00	1.00
30–<60	217	1.16 (0.97 to 1.39)	1.08 (0.90 to 1.29)	0.97 (0.80 to 1.18)
≥60	188	1.65 (1.37 to 1.99)	1.47 (1.21 to 1.78)	1.10 (0.87 to 1.39)*
P trend		<0.001	<0.001	0.51
<b>Disease mortality</b>				
≤30 (Ref.)	270	1.00	1.00	1.00
30–<60	204	1.19 (0.99 to 1.43)	1.10 (0.92 to 1.33)	0.98 (0.81 to 1.20)
≥60	177	1.71 (1.41 to 2.08)	1.52 (1.25 to 1.85)	1.11 (0.87 to 1.42)
P trend		<0.001	<0.001	0.48
<b>CVD mortality</b>				
≤30 (Ref.)	138	1.00	1.00	1.00
30–<60	105	1.19 (0.92 to 1.54)	1.09 (0.84 to 1.41)	0.91 (0.69 to 1.20)
≥60	96	1.62 (1.24 to 2.12)	1.43 (1.09 to 1.88)	0.89 (0.63 to 1.25)†
P trend		0.001	0.01	0.47
<b>Non-CVD mortality</b>				
≤30 (Ref.)	157	1.00	1.00	1.00
30–<60	112	1.14 (0.89 to 1.45)	1.08 (0.84 to 1.38)	1.08 (0.83 to 1.41)
≥60	92	1.55 (1.19 to 2.02)	1.42 (1.08 to 1.85)	1.33 (0.96 to 1.86)‡
P trend		0.002	0.02	0.11
<b>Cancer mortality</b>				
≤30 (Ref.)	76	1.00	1.00	1.00
30–<60	59	1.21 (0.86 to 1.71)	1.15 (0.82 to 1.64)	1.13 (0.78 to 1.64)
≥60	42	1.43 (0.98 to 2.10)	1.31 (0.89 to 1.94)	1.21 (0.75 to 1.98)§
P trend		0.06	0.17	0.42

Model 1: FLI category, examination date, age, family history of diabetes, family history of cardiovascular disease, smoking status, alcohol consumption, physical activity, fruit, berry & berry consumption (and CVD history for CVD mortality) (and cancer history for cancer mortality).  
Model 2: Model 1 plus C reactive protein, fibrinogen, leucocytes and thrombocytes.

Model 3: Model 2 plus systolic blood pressure, diastolic blood pressure, insulin, fasting glucose, LDL, HDL.

\*All-cause mortality: Other independent predictors were age, smoking pack years, alcohol consumption, fibrinogen, leucocyte count, systolic blood pressure and glucose.

†CVD mortality: Other independent predictors were age, smoking pack years, alcohol consumption, fibrinogen, leucocyte count, systolic blood pressure and glucose.

‡Non-CVD mortality: Other independent predictors were age, smoking pack years, alcohol consumption, leucocyte count and glucose.

§Cancer mortality: Other independent predictors were age, smoking pack years and thrombocyte count.

¶Disease mortality: Other independent predictors were age, smoking packyears, alcohol consumption, fibrinogen, leucocyte count, systolic blood pressure and glucose.

\*\*Statistically significant at  $p \leq 0.05$ .

CVD, cardiovascular disease; FLI, fatty liver index; Ref, reference.

metabolic factors and therefore increase in cardiovascular mortality and possibly, overall mortality.<sup>36</sup>

Our data appear to suggest that FLI prediction of cancer mortality is connected partly with high alcohol consumption and partly related to FLD. However, alcohol consumption was not an independent predictor in our models (table 2). Rather, pack years of smoking, which is highly correlated with alcohol consumption, was an independent predictor of cancer mortality.

Our study has some limitations. First, we are unable to observe the influence of gender on these associations

because our study population comprised of men only. However, Bedogni *et al*<sup>21</sup> concluded that the influence of gender in FLI was related to insulin and skinfold thickness and was probably insignificant. Second, there are possibly uncontrolled confounding due to unmeasured confounders, and there is the possibility of residual confounding due to incomplete measurements of potential confounders.

Another important limitation of this study is that FLI used here, as a surrogate of fatty liver does not measure severity of FLD. Furthermore, data on serum



transaminases (aspartate transaminase and alanine transaminase) are not available. Indeed, these transaminases are component variables in the calculation of simple fibrosis biomarkers such as APRI and FIB-4.<sup>37</sup> Increases in these markers are related to increasing severity and progression of FLD to fibrosis. Such increases are also associated with liver-related mortality and all-cause mortality in patients with chronic liver disease.<sup>9</sup> Therefore, we are unable to compare the prognostic value of FLI with the prognostic value of the fibrosis biomarkers.

It should be noted also that the hepatitis B and hepatitis C statuses of the subjects were not established at recruitment. Although the prevalence rate of hepatitis B<sup>38</sup> and hepatitis C<sup>39</sup> have remained low in the Finnish population, routine screening tests for hepatitis B became available since the early 1980s<sup>40</sup> shortly before the onset of subject recruitment. Similarly, screening test for hepatitis C was available since 1989,<sup>41</sup> around the end of recruitment. Baseline hepatitis B and hepatitis C screening tests, which could further strengthen the results, were not conducted on the subjects.

We should also acknowledge that, Eastern Finland, the region where the KIHD subjects were drawn from, is a relatively ethnically homogenous population. An extrapolation of this fact to the KIHD is well founded. However, specific data on ethnicity, which could buttress this, were not collected and our judgement of relative ethnical homogeneity of our study sample is an inference based on this fact.

The strengths of our study include the prospective design with adequate follow-up and a large number of deaths, which allowed us to demonstrate the prospective associations of FLD with the mortality outcomes. We have adjusted for a range of possible confounders and are able to specifically observe the effects of different categories of factors on the associations of FLD with mortality outcomes.

In conclusion, FLD, as defined by FLI, was associated with increased risk of all-cause, CVD and non-CVD mortality independent of baseline constitutional risk factors, life-style risk factors and inflammatory risk factors, suggesting that the association of fatty liver with extrahepatic morbidity has significant impact on overall mortality outcomes. However, the association of FLD with risk of CVD mortality is remarkably affected by the baseline metabolic factors. This bears on estimated risks for mortality outcomes incorporating CVD mortality, especially in population with higher incidence of CVD mortality.

Our findings have important implications for screening and surveillance strategies. Amid the epidemic of FLD, association of FLD with mortality outcomes suggests that early detection and management can be highly beneficial. People with high FLI should be further evaluated for FLD, FLD severity and FLD progression. They should also be evaluated and monitored for subclinical or overt metabolic, cardiovascular and non-CVD.

In such persons, appropriate preventive or treatment measures should be instituted in order to improve their prognoses.

**Authors contributions** OOO and T-PT conceived the study, OOO and T-PT designed the study. OOO performed the statistical analyses. OOO wrote the first draft of the manuscript. OOO, JKV, JP and TPT contributed to the development of the manuscript and reviewed the manuscript. OOO, JKV, JP and TPT approved the final draft of the manuscript.

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