European Journal of Internal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Relationships between education and non-alcoholic fatty liver disease

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ARTICLE INFO

Keywords:
Non-alcoholic fatty liver disease
Education
ISCED
Fibrosis 4- index
Fatty liver index
Liver stiffness
Paracelsus 10,000 cohort study
Socioeconomic status

ABSTRACT

Introduction: Individuals with lower levels of education are at a higher risk of developing various health conditions due to limited access to healthcare and unhealthy lifestyle choices. However, the association between non-alcoholic fatty liver disease (NAFLD) and educational level remains unclear. Therefore, the aim of this study was to investigate whether there is an independent relationship between NAFLD and educational level as a surrogate marker for socioeconomic status (SES).

Methods: This cross-sectional study included 8,727 participants from the Paracelsus 10,000 study. The association between NAFLD and educational level was assessed using multivariable logistic regression models and multivariable linear regression. The primary endpoints were NAFLD (FLI score > 60) and liver fibrosis (FIB-4 score > 1.29). Further subgroup analysis with liver stiffness measurement was done.

Results: In the study, NAFLD prevalence was 23% among participants with high education, 33% among intermediate, and 40% among those with low education ($p<0.01$). Importantly, a significantly reduced risk of NAFLD was observed in individuals with higher education, as indicated by an adjusted relative risk of 0.52 ($p < 0.01$). Furthermore, higher education level was associated with significantly lower odds of NAFLD and fibrosis. Additionally, a subgroup analysis revealed that higher liver stiffness measurements were independently associated with lower levels of education.

Conclusion: The study's findings indicate that a lower education level increases the risk of NAFLD independent of confounding factors. Therefore, these findings highlight the potential impact of educational attainment on NAFLD risk and emphasize the need for targeted interventions in vulnerable populations.

1. Introduction

Affecting up to 30% of the adult population in western countries, non-alcoholic fatty liver disease (NAFLD) is a worldwide public health problem [1,2]. Because 5% of individuals with NAFLD suffer from steatohepatitis, cirrhosis and hepatocellular carcinoma, NAFLD is not

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https://doi.org/10.1016/j.ejim.2023.07.039
Received 12 April 2023; Received in revised form 25 July 2023; Accepted 27 July 2023

only a global healthcare problem but is also associated with a high clinical and economic burden [2,3]. In addition, NAFLD has been shown to be associated with high risk for cardiometabolic diseases, extrahepatic malignancy, diabetes and lung diseases [4–6]. Despite its high burden, screening for NAFLD remains a controversial topic, and there is a lack of clarity on the most effective screening strategies [7].

Recent research has shown that a low socioeconomic status (SES) have been linked to poor health outcomes, including increased risk of chronic diseases such as heart disease and diabetes [8–10]. This may be due to factors such as limited access to healthcare, unhealthy living conditions, poor nutrition, and exposure to environmental hazards [11]. As a result, addressing the socioeconomic determinants of health is critical for reducing health disparities and improving overall population health [11].

However, it is unclear whether this association between low SES, education and poor health outcomes also applies to NAFLD.

A few studies have highlighted the significant association between education level and the risk of developing NAFLD [12,13]. An overview of different studies focusing on NAFLD and education are given in the supplemental material Table 1. The authors argue that individuals with lower education levels tend to have a higher prevalence of risk factors associated with NAFLD, such as poor dietary choices, sedentary lifestyles, and limited access to healthcare resources [12]. Another argument is that limited educational attainment often leads to a lack of awareness regarding liver health [14]. Higher education levels, on the other hand, have been linked to a greater understanding of the importance of maintaining a healthy lifestyle and making informed choices [14]. Although the association between education level and NAFLD has been investigated in a few studies, there is limited research on this topic in a population based cohort.

Recent research has shown that the education level can also be used as surrogate marker for SES. [15–17] The level of education can be easily defined through self-reported survey, making it a more available and comparable marker of socioeconomic status [16]. Additionally, the use of education level as a marker of socioeconomic status allows a direct comparison between different populations, as education is a more universal parameter in comparison to income or occupation [16]. Furthermore it is not affected by regional differences [16,15]. Therefore, the International Standard Classification of Education (ISCED) was conceived as a sophisticated framework to categorize educational attainment and define the degree of education in populations across the world [18]. This globally recognized index provides a comprehensive understanding of educational systems, allowing for comparability and standardization of educational data between countries [18]. The generalized ISCED (GISCED) takes this one step further by proposing a standardized framework for categorizing education levels in survey data, simplifying the comparison of education data collected in different countries and sources. This approach allows trichotomized groups of low, middle, and high ISCED categories [18].

In this study, the assessment of steatosis and hepatic fibrosis was conducted through the use of the fatty liver index (FLI) and the fibrosis-4 index (FIB-4) [19,20]. These surrogate markers have been shown to be effective in population-based settings and provide reliable results [19,21]. The subgroup analysis also incorporated liver stiffness measurement (LSM) data, which is a non-invasive and highly accurate method for assessing liver fibrosis in patients with NAFLD [22]. The high correlation between LSM and liver biopsy further strengthens its utility as a surrogate marker [22].

The objective of this study was to examine the relationship between NAFLD and educational attainment, as represented by the ISCED, within a population-based high-risk cohort. The hypothesis of the current study is that lower education levels, as a proxy for lower socioeconomic status, are associated with a higher risk of NAFLD and liver fibrosis. Furthermore, the study aims to investigate the independent association between education level and NAFLD/liver fibrosis, after adjusting for age, sex, metabolic syndrome, income, employment and marital status. To gain a comprehensive understanding, multifaceted approach was used to evaluated the relationship between ISCED and NAFLD, including measures of liver steatosis (FLI score) liver fibrosis (FIB-4 score) and liver stiffness measurement.

Table 1
Table presents a comparison of various demographic and clinical characteristics among three educational levels (Low ISCED, Middle ISCED, High ISCED) within the overall study population. P-values are provided to indicate the statistical significance of differences between groups.

N	Low ISCED $N = 681$	Middle ISCED $N = 6037$	HIGH ISCED $N = 2009$	P value
Sex male [%] (*n*)	39% (264)	48% (2891)	51% (1020)	< 0.001
Age [years] (SD.)	58 (8)	56 (8)	54 (8)	< 0.001
BMI [kg/m2] (SD.)	28 (5)	27 (5)	25 (4)	< 0.001
Weight [kg] (SD.)	78 (16)	78 (16)	76 (15)	< 0.001
Waist circumference [cm] (SD.)	96 (13)	94 (13)	91 (12)	< 0.001
Diabetes Mellitus [%] (n)	7% (47)	3% (209)	2% (42)	< 0.001
Hypertension (yes) [%] (*n*)	35% (237)	22% (1341)	16% (312)	<0.001
Metabolic syndrome [%] (*n*)	24% (165)	17% (1038)	11% (223)	< 0.001
ALT [U/l] (SD.)	26 (17)	25 (14)	25 (16)	0.30
AST [U/l] (SD.)	25 (11)	24 (10)	24 (10)	0.60
GGT [U/l] (SD.)	31 (34)	32 (44)	29 (27)	0.014
HbA1c [%] (SD.)	5.6 (0.6)	5.5 (0.5)	5.4 (0.4)	<0.001
Total cholesterol [mg/dl] (SD.)	213 (41)	210 (38)	210 (38)	0.12
Triglycerides [mg/dl] (SD.)	126 (74)	116 (80)	107 (62)	<0.001
HDL [mg/dl] (SD.)	61 (17)	64 (18)	65 (18)	<0.001
LDL [mg/dl] (SD.)	144 (39)	141 (36)	141 (36)	0.09
Platelets [G/l] (SD.)	252 (60)	250 (55)	247 (54)	0.08
Fib4 ≥1.3 [%] (n)	35% (214)	31% (1678)	28% (523)	0.01
FLI≥60 [%] (n)	40% (259)	33% (1877)	23% (436)	<0.001
House income (per month)				<0.001
0 up to 1000 euro	19% (128)	7% (448)	3% (62)	
1001–2000 euros	47% (318)	35% (2092)	16% (313)	
2001–3000 euros	15% (100)	26% (1554)	26% (520)	
3001–4000 euros	4% (24)	13% (792)	18% (362)	
4001–5000 euros	2% (11)	7% (409)	14% (277)	
> 5000 euros	1% (7)	4% (213)	14% (289)	
No response	14% (93)	9% (529)	9% (186)	
Employment status				<0.001
unemployed	6% (39)	2% (147)	2% (32)	
student	0% (0)	0% (7)	0% (7)	
military service	0% (1)	0% (0)	0% (0)	
civilian service	4% (25)	2% (124)	2% (38)	
retired	48% (324)	28% (1677)	17% (338)	
employed	43% (292)	68% (4082)	79% (1594)	
Relationship type				<0.001
married, living together	61% (416)	62% (3755)	64% (1295)	
married, living seperated	1% (9)	1% (88)	1% (27)	
partnership	5% (31)	8% (458)	9% (184)	
divorced	12% (79)	11% (689)	12% (245)	
single	14% (98)	14% (836)	11% (216)	
widowed	6% (42)	3% (184)	1% (27)	
non response	1% (6)	0% (27)	1% (15)	

Abbreviations: ISCED: International Standard Classification of Education; N: number, SD: standard deviation; BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; FLI Score: fatty liver index; FIB-4 Index: Fibrosis-4 Index.

2. Methods

In this study, data from 10,044 participants were collected between 2013 and 2020 and entered into the Paracelsus 10,000 registry [23]. The Paracelsus 10.000 study is a large population-based study conducted in Salzburg, Austria, aimed at investigating the determinants of chronic diseases and the impact of lifestyle factors on health outcomes [23]. This group contained an equal distribution of women and men between 40 and 77 years of age [23]. The recruitment process for the Paracelsus 10, 000 study aimed to randomly select participants from the population in and around the city of Salzburg based on the Austrian national register of residents [23]. Approximately 60,000 invitation letters were distributed, and a total of 10,044 participants were examined [23]. Participation in the study was voluntary, and participants did not receive any financial rewards [23]. However, they did benefit from a preventive medical check-up [23]. The recruitment process ensured a diverse sample by randomly selecting participants and including both men and women across different age ranges [23]. Data collection was conducted through a combination of self-administered questionnaires, physical measurements, and biological sample collection [23]. Participants completed a detailed questionnaire on lifestyle factors, including diet, physical activity, smoking, and alcohol consumption [23]. Anthropometric measurements, such as height, weight, and waist circumference, were taken, and blood and urine samples were collected for biomarker analysis [23]. All measurements were performed by trained and certified staff using standardized protocols and calibrated equipment [23].

In a subsequent step, patients were randomly selected for a subgroup analysis, during which they underwent a LSM by Fibroscan procedure [23]. The guidelines for ethics and data management corresponded to local standards, and the study was performed in accordance to the standards of the Declaration of Helsinki. The study was approved by the local ethics committee (number 415- E/1521/6–2012). A detailed explanation of all figures and tables is provided in the supplemental material.

2.1. Inclusion and exclusion criteria

Fig. 1 shows a flow chart with the inclusion and exclusion criteria. Fig. 2 shows a flow chart for subgroup analysis. A detailed description of Figs. 1 and 2 is provided in the supplementary material. The current investigation defined strict inclusion criteria to ensure the integrity of the study's findings. Specifically, the study included only those individuals between the ages of 40 and 69 who provided documentation of assessments for FLI and FIB-4, as well as GISCED score and supplied data regarding income, employment, and marital status. Individuals who were missing any of the mentioned scores were excluded from the study. Exclusion criteria were viral hepatitis or excessive alcohol consumption (>40 g in females and >60 g in males). For subgroup analysis

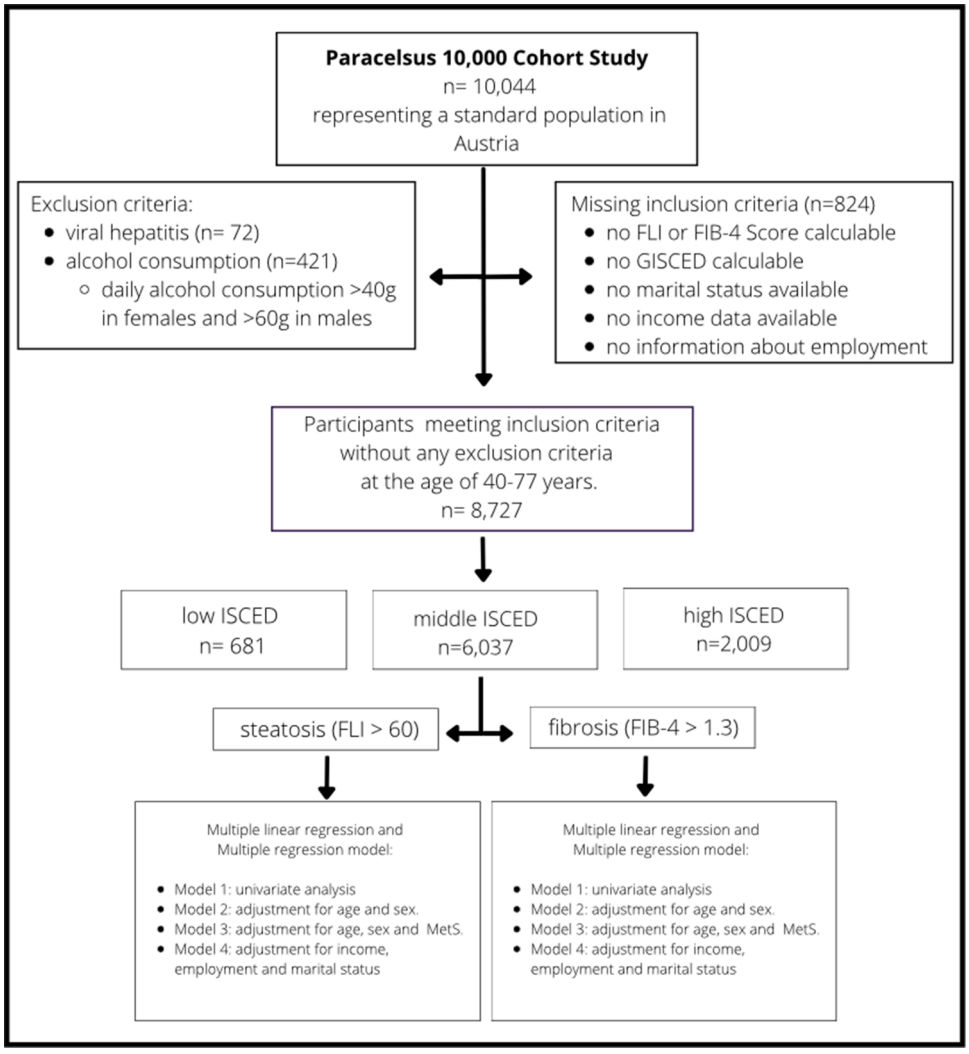

Fig. 1. Flow chart showing Inclusion and exclusion criteria of cross-sectional data analysis. Abbreviations: FLI: fatty liver index, FIB-4 Score: fibrosis-4 index, GISCED, N: number and MetS: metabolic syndrome.

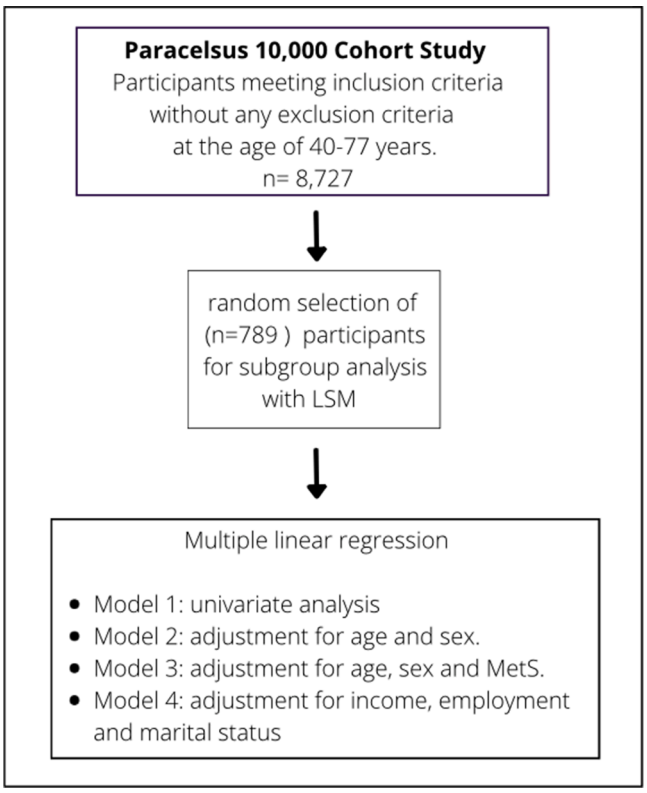

Fig. 2. Flow chart illustrating the process of participant selection for subgroup analysis by LSM data. Abbreviations: N: number, LSM: lifer stiffness measurement and MetS: metabolic syndrome.

participants were randomly selected. The same inclusion and exclusion criteria were applied with an additional liver stiffness measurement (n = 789).

2.2. Definition of terms

NAFLD was identified using a scoring system called the FLI score. A score $\geq$ 60 was considered elevated, according to the criteria set by Bedogni et al. [19,23]. Liver fibrosis was expressed by the FIB-4 score, which is a well-validated, non-invasive assessment of liver fibrosis biomarkers (age $\times$ AST [IU/L]/platelet count [$\times$ 10^9/L] $\times$ $\sqrt{}$ALT [IU/L]) [20,23]. With a cut-off less than 1.3, significant fibrosis is reliably excluded [20,23].

Liver stiffness measured by kilopascals (kPA) was used as continuous parameter. Education level was used as the indicator for SES. Subjects were divided into the following groups: (i) those with a low education level (less than a high-school education), (ii) those with an intermediate education level (from high school to less than university or college degree) and (iii) those with a high education level (university or college degree) according to the generalized International Standard Classification of Education (GISCED) [23,24]. All participants had their anthropometric, clinical, and laboratory parameters recorded. MetS was defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III). [23,25] Therefore, MetS was defined by three out of the following five criteria: (i) central obesity, (ii) hypertriglyceridemia, (iii) HDL cholesterol level, (iv) hypertension and (v) a fasting glucose $\geq$ 6.1 mmol/L [23,25]. Diabetes was characterized by HbA1c $>$ 6.4% or the use of insulin or glucose-lowering medications. Alcohol consumption was defined by gram per day by self-reporting questionnaires. Additionally, patients employment, marital status, and income were documented by self-reporting questionairs. The participants' employment status was classified into six categories: [1] employed [2] unemployed, [3] student, [4], military service, [5] civilian service, [6] retired. The participants' marital status was categorized as follows: [1] married, living together, [2] married, living separately, [3] partnership, [4] divorced, [5] single, [6] widowed, [7] no response. Participants were asked to provide an estimate of their approximate monthly net household income in the following categories: [1] Up to 1000 euros, [2] 1001–2000 euros, [3] 2001–3000 euros, [4] 3001–4000 euros, [5] 4001–5000 euros, [6] Above 5000 euros, and [7] no response.

2.3. Statistics

We analyzed continuous parameters using mean and standard deviation (SD), and calculated p-values using the student's t-Test. Categorical data were expressed as percentages and compared using chi-squared tests, with a significance level of $p < 0.01$.

The research in this study is dedicated to conducting an etiological investigation [26]. Therefore, the primary finding of the study was to address the etiological question of NAFLD in relation to education through relative risk analysis. Both crude and adjusted models were calculated, with particular focus on the age- and sex-adjusted model (model 2). This choice was based on the independence of these variables from the primary outcome. We used logistic regression to calculate beta coefficients. Based on these, adjusted risk ratios were calculated using the "adjrr" command in Stata [27]. The "adjrr" command uses the "margins" command with the (at) function. The "margins" command produces estimates based on predictions.

Additionally, the study incorporated exploratory statistical analyses, including linear and logistic regression models. These statistical models were calculated for descriptive purposes.

The liver stiffness measurement (LSM), FLI score, and FIB-4 score were used as continuous variables in the linear regression analysis, and liver steatosis (NAFLD = FLI score $\geq$ 60) and liver fibrosis (FIB-4 score $\geq$ 1.3) were used as dependent variables in the logistic regression analysis.

The ISCED category was used as the primary exposure and independent variable, with low ISCED serving as the reference category for comparison with intermediate and high ISCED. Model 1 was a univariate association between the primary exposure (ISCED category) and the dependent variable. In Model 2, we adjusted for the covariables of age and sex, in Model 3, we included additionally metabolic syndrome and in model 4 we adjusted for income, marital status and employment. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for the binary dependent variables, and regression coefficients (r) and 95% CIs for the continuous dependent variables. The liver stiffness measurement (LSM), FLI score, and FIB-4 score were used as continuous variables in the linear regression analysis, and liver steatosis (NAFLD = FLI score $\geq$ 60) and liver fibrosis (FIB-4 score $\geq$ 1.3) were used as dependent variables in the logistic regression analysis.

All statistical analyses were conducted using the Stata/IC 17 software package.

3. Results

A total of 8727 participants with an assessment of ISCED, FLI and FIB-4 scores were included in this study. We first compared patients with low (n = 681), mild (n = 6037) and high (n = 2009) ISCED scores. The demographic characteristics of these groups are shown in Table 1. There was a significant difference concerning data such as BMI, weight and waist circumference. Moreover, all three groups significantly differed regarding health-related factors such as type 2 diabetes (T2D), hypertension and MetS. Among the three ISCED groups (low ISCED, middle ISCED and high ISCED), there was a significant difference regarding different blood markers such as HbA1c, triglycerides and HDL. HbA1c and triglyceride levels were higher in the low-ISCED group and lower in participants with higher levels of education. HDL levels were highest in the high-ISCED group. Regarding liver steatosis, the FLI score was highest in participants with lower education levels (FLI = 49 in the low-ISCED group vs. FLI = 35 in the high-ISCED group; $p < 0.01$).

Participants in the low-ISCED group had more frequent liver fibrosis (FIB-4 score ≥ 1.3) than those with a higher education level ($p = 0.01$). Results show that there are notable differences in income, employment status and relationship type based on education level. Higher education levels were associated with higher income, higher employment rates, and a higher likelihood of being married and living together. A table comparing descriptive statistic of the LSM subgroup in comparison to the overall group will be provided in the supplemental material Table 2.

3.1. Association between steatosis and ISCED

The associations between educational status and the risk of NAFLD were examined using various models. The adjusted relative risks (adjustment for age and sex) were estimated for the middle and high ISCED group, as well as for the crude relative risk (RR). The results showed that individuals with medium education level (middle ISCED group) had a significantly lower risk of NAFLD compared to the reference group, with an aRR of 0.77 (95%CI 0.70–0.85, $p < 0.01$). Similarly, individuals with higher education exhibited a significantly reduced risk of NAFLD. In the middle ISCED group the crude RR was 0.80 (95% CI 0.72–0.89, $p < 0.01$). Similarly, when considering the high ISCED group, the RR was 0.54 ($p < 0.01$). Results are shown in Table 2.

Linear regression models and logistic regression models were calculated. Results are shown in Table 3. In the univariate linear regression analysis, participants in the high-ISCED group had lower FLI compared to those in the low-ISCED group. (*r*: –14.16 [–16.72 to –11.60]; $p < 0.01$). The same applied for patients in the intermediate-ISCED group compared to participants with the lowest education levels (r: –7.04 [–9.37 to –4.70]; $p < 0.01$). Significance of the linear regression coefficient remained after forcing sex, age (model 2), MetS (model 3) and income, employment, and marital status (model 4) into the system.

The same models were used to calculate ORs from categorical outcomes with an FLI score ≥ 60. In the low ISCED group 259 (40%), in de middle ISCED group 1877 (33%) and in the high ISCED group 436 (23%) of participants had a FLI Score ≥ 60 respectively ($p<0.01$). In the univariate analysis, participants with a high education level exhibited a significantly lower OR (FLI score ≥ 60, OR 0.43, 95% CI 0.36–0.52, $p \leq 0.01$) for liver steatosis compared to those in the low-ISCED group. The same applied for participants in the intermediate-ISCED group compared to the low-ISCED group (FLI score ≥ 60, OR 0.71, 95% CI 0.61–0.84, $p \leq 0.01$). After adjustment for sex and age in model 2 and adjustment for sex, age and MetS in model 3, a significantly lower OR for liver steatosis was observed in the intermediate-and high-ISCED groups compared to participants with low education levels. In Model 4, we adjusted for income, employment, and marital status showing significantly lower Odds of NAFLD for the Intermediate ISCED group (OR of 0.73, 95% CI: 0.59–0.90, $p \leq 0.01$) and high ISCED group (OR of 0.46 95% CI: 0.36–0.59, $p \leq 0.01$) compared the low ISCED group.

Table 2
Relative Risk analysis with liver steatosis as primary endpoint and educational status as categorical fixed effect, with lower education as the reference category.

	Relative Risk estimation (FLI > 60)		
	Low ISCED	Intermediate ISCED	High ISCED
Model 1	Ref.	0.80 (95% CI 0.72–0.89, $p < 0.01$)	0.54 (95% CI 0.47, 0.62, $p < 0.01$)
Model 2	Ref.	0.77 (95%CI 0.70–0.85, $p < 0.01$)	0.52 (95% CI 0.45- 0.59, $p < 0.01$)

Model 1 shows the univariate crude RR.
Model 2 shows aRR for age and sex.
Abbreviations: FLI: fatty liver index; RR: relative Risk; aRR: adjusted relative Risk; CI: confidence interval.

Table 3
Multiple linear and logistic regression with liver steatosis as primary endpoint and educational status as categorical fixed effect, with lower education as the reference category.

	Linear regression			Logistic regression FLI ≥ 60	
	Low ISCED	Intermediate ISCED Regression coefficient (95% CI, *p*-value)	High ISCED Regression coefficient (95% CI, *p*-value)	Intermediate ISCED OR (95% CI, *p*-value)	High ISCED OR (95% CI, *p*-value)
Model 1	Ref	–7.04 (–9.37 to –4.70) $p \leq 0.01$	– 14.16 (–16.72 to –11.60) $p \leq 0.01$	0.71 (0.61–0.84) $p \leq 0.01$	0.43 (0.36–0.52) $p \leq 0.01$
Model 2	Ref	–7.61 (–9.74 to –5.48) $p \leq 0.01$	–14.56 (–16.91 to –12.21) $p \leq 0.01$	0.65 (0.54–0.77) $p \leq 0.01$	0.38 (0.31–0.46) $p \leq 0.01$
Model 3	Ref	–5.21 (–6.99 to –3.43), $p \leq 0.01$	–9.97 (–11.93 to –8.01), $p \leq 0.01$	0.71 (0.58–0.87) $p \leq 0.01$	0.44 (0.35–0.56) $p \leq 0.01$
Model 4	Ref	−4.94 (−6.75 to −3.14) $p \leq 0.01$	−9.64 (−11.69 to −7.60) $p \leq 0.01$	0.73 (0.59–0.90) $p \leq 0.01$	0.46 (0.36 – 0.59) $p \leq 0.01$

Model 1 shows the univariate crude regression coefficient / OR for FLI ≥ 60.
Model 2 shows regression coefficient / OR after adjustment for age and sex.
Model 3 shows regression coefficient / OR after adjustment for age, sex and MetS.
Model 4 shows regression coefficient / OR after adjustment for income, employment and marital status.
Abbreviations: FLI: fatty liver index; FIB-4: fibrosis-4 index; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.

3.2. Association between fibrosis and ISCED

Results of the association between liver fibrosis (FIB-4 > 1.29) are shown in Table 4. In the univariate linear regression analysis, participants in the high-ISCED group evidenced lower likelihood for fibrosis reflected by lower Fib-4 scores, compared to those in the low-ISCED group (r: –0.10 [–0.15 to –0.05]; $p < 0.01$). The same applied for participants in the intermediated- ISCED group compared to those with the lowest education levels (r: –0.08 [–0.13 to –0.04]; $p < 0.01$) . However, there was not a significantly lower regression coefficient between the intermediate- and high-ISCED groups compared to participants with lowest education levels after forcing model 2 and model 3 into the system.

The same models were used to calculate ORs from categorical outcomes with a FIB-4 score ≥ 1.3. In the low ISCED group 214 (35%), in the middle ISCED group 1678 (31%) and in the high ISCED group 523 (28%) of participants had a FIB-4 ≥ 1.3 respectively. In the univariate analysis, there was a significantly lower OR for liver fibrosis (FIB-4 score ≥ 1.3, OR 0.75, 95% CI 0.62–0.90, $p<0.004$) among participants with a high education level compared to those in the low-ISCED group. This trend was also shown in participants in the intermediate-ISCED group compared to the low-ISCED group (FIB-4 ≥ 30, OR 0.85, 95% CI 0.72–1.02, $p < 0.079$). However, this trend did not reach statistical significance. After adjustment for age and sex (model 2) and adjustment for age, sex and MetS, (model 3), participants with intermediate and high education levels did not demonstrate significantly lower ORs for fibrosis compared to those in the low-ISCED group. The same applied for model 4 (adjustement for income, marital status and employment).

3.3. Association between LSM and ISCED

Subgroup analysis of 789 participants in whom data on LSM were available, linear regressions models have shown that a high-ISCED was

Table 4
Multiple linear and logistic regression with liver fibrosis as primary endpoint and the educational status as categorical fixed effect, with lower education as the reference category.

	Linear regression			Logistic regression FIB-4 ≥ 1.3	
	Low ISCED	Intermediate ISCED Regression coefficient (95% CI, *p*-value)	High ISCED Regression coefficient (95% CI, *p*-value)	Intermediate ISCED OR (95% CI, *p*-value)	High ISCED OR (95% CI, *p*-value)
Model 1	Ref	–0.08 (–0.13 to –0.04) $p \leq 0.01$	–0.10 (–0.15 to –0.05) $p \leq 0.01$	0.85 (0.72–1.02) $p = 0.079$	0.75 (0.62–0.90) $p \leq 0.004$)
Model 2	Ref	–0.02 (–0.06 to 0.02) $p = 0.22$	–0.00002 (–0.04 to 0.04) $p = 0.80$	1.20 (0.98–1.46) $p = 0.15$	1.24 (0.99–1.54) $p = 0.09$
Model 3	Ref	0.02 (–0.06 to 0.02) $p = 0.50$	0.005 (–0.05 to 0.04) $p = 0.14$	1.16 (0.92–1.47) $p = 0.21$	1.18 (0.91–1.52) $p = 0.21$
Model 4	Ref	−0.01 (−0.06 to 0.03) $p = 0.50$	0.01 (−0.03 to 0.06) $p = 0.57$	1.20 (0.98–1.47) $p = 0.08$	1.27 (1.01–1.60) $p = 0.06$

Model 1 shows the univariate crude regression coefficient /OR for FIB-4 ≥ 1.3.
Model 2 shows regression coefficient / aOR after adjustment for age and sex.
Model 3 shows regression coefficient / aOR after adjustment for age, sex and MetS.
Model 4 shows regression coefficient/ OR after adjustment for income, employment and marital status.
Abbreviations: FLI: fatty liver index; FIB-4: fibrosis-4 index; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.

associated with a lower liver stiffness compared to those in the low-ISCED group (*r*: –1.40 [–2,53 to –0.26]; $p < 0.02$). The same applied for patients in the intermediate-ISCED group compared to participants with the lowest education levels (*r*: –1.23 [–2.27 to –0.20]; $p < 0.01$). This trend remained after forcing sex, age into the system. In model 4, which adjusted for income, employment, and marital status, the regression coefficients remained significant for both the Intermediate ISCED group (−1.48, 95% CI: −2.55 to −0.41, $p < 0.01$) and the high ISCED group (−1.54, 95% CI: −2.54 to −0.41, $p = 0.012$). Data are shown in Table 5.

Table 5
Multiple linear and logistic regression with liver stiffness as primary endpoint and the educational status as categorical fixed effect, with lower education as the reference category.

	Linear regression		
	Low ISCED	Intermediate ISCED Regression coefficient (95% CI, *p*-value)	High ISCED Regression coefficient (95% CI, *p*-value)
Model 1	Ref	–1.23 (–2.27 to –0.20) $p < 0.01$	– 1.40 (–2.53 to –0.26) $p = 0.02$
Model 2	Ref	–1.35 (–2.38 to –0.32) $p < 0.01$	–1.53 (–2.66 to –0.40) $p < 0.01$
Model 3	Ref	–1.46 (–2.49 to –0.43) $p = 0.05$	–1.53 (–2.66 to –0.41) $p = 0.08$
Model 4	Ref	−1.48 (−2.55 to – 0.41) $p<0.01$	−1.54 (−2,54 to −0.41) $p = 0.012$

Model 1 shows the univariate crude regression coefficient for LSM.
Model 2 shows regression coefficient after adjustment for age and sex.
Model 3 shows regression coefficient after adjustment for age, sex and MetS.
Model 4 shows regression coefficient after adjustment for income, employment and marital status.
Abbreviations: FLI: fatty liver index; FIB-4: fibrosis-4 index; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.

4. Discussion

In this population-based cohort study with 8727 participants, the connection between educational status (represented by ISCED) and the risk of NAFLD was examined. We found that individuals with high ISCED exhibited a significantly reduced risk of liver steatosis, with a substantial 46% lower risk compared to the low ISCED group. In Model 2, individuals with high ISCED experienced a remarkable 48% lower risk of liver steatosis (aRR = 0.52, 95% CI 0.45–0.59, $p < 0.01$), after adjusting for age and sex. These results emphasize that higher education levels, represented by intermediate and high ISCED groups, are associated with a substantial reduction in the risk of developing liver steatosis, even after accounting for confounding factors. Furthermore, this study, one of the largest to date, underscores the influence of educational attainment on liver health and underscores the importance of taking into account educational status as a proxy for socioeconomic status when evaluating the risk of NAFLD. The study also found that liver stiffness measurement decreases with higher educational status, further supporting the link between education and liver health. Overall, patients with low educational status showed signs of poorer health. However, the relationship between education and liver health was found to be independent of other factors such as age, gender and metabolic syndrome, income, employment and marital status in multivariable regression models. These findings underline the importance of this study and the need for further investigation into the relationship between education and NAFLD.

Results of the current study are in line with growing evidence from previous studies showing that SES is an important risk factor influencing the prevalence of NAFLD [6,23,28]. SES describes the position of an individual on a socioeconomic scale that is represented by a combination of income, education, heritage and living space [23,29,30]. Previous studies have shown that education level has the highest impact on the SES and is therefore a common and frequently used surrogate marker [23,31]. As this study has found that a low ISCED level is associated with liver steatosis, these data are in line with other studies showing that a low educational status is associated with several unfavorable health outcomes [23,32–34].

Eduardo Vilar-Gomez et al. showed that in addition to the impact of high-quality diet and physical activity on NAFLD incidence, a higher educational attainment was associated with a reduced risk of NAFLD compared to individuals with lower levels of education [12,23]. This association remained statistically significant even after accounting for various confounding factors [12,23]. On the other hand, they were not able to show this association among different income groups, although those with a high income tended to have a lower prevalence of NAFLD after adjusting for age [12,23]. Nevertheless, higher educational levels and high income were linked to healthier dietary habits and increased physical activity [12,23].

In another study NAFLD has been associated with several independent risk factors, including male gender, urban living, hypertension, high BMI, waist circumference, serum triglyceride levels, and fasting blood sugar levels [13,23]. However, education has been identified as a protective factor against NAFLD. The author draws the conclusion that NAFLD is potentially influenced by one's educational background, which could be attributed to individuals with higher education levels being more conscious of their health [13,23]. They further argue that those with higher education levels are more inclined to make dietary adjustments and engage in regular exercise to prevent obesity, which in turn may contribute to a lower prevalence of NAFLD [13,23].

It is ample evidence that the main drivers of NAFLD incidence associated with SES are insulin resistance, obesity and lipid metabolic disorders [6,23,35]. This observation is in accordance with data from the current study showing that participants in the low-ISCED group had T2D and a MetS more often compared to those in higher-ISCED groups.

Moreover, patients with a lower education level had higher BMI levels compared to those in the high-ISCED group. Goodman et al. have also reported higher BMI and increased insulin resistance in subjects with lower SES [23,36]. Observations from another recent study have shown that subjects with low SES have higher triglyceride (TG), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels than patients with high SES [5,23]. From our data, the low-SES group had higher TG and HbA1c levels but no significant difference in transaminase levels. Nevertheless, the calculated FLI score was significantly higher in those with lower education levels compared to the high-ISCED group, indicating that a low education level is risk factor for liver steatosis (FLI score 50 vs. 36 in the low-ISCED group vs. the highest-ISCED group, respectively, $p \leq 0.01$). Moreover, linear regression models from this study showed that participants in the high-ISCED group had a significantly lower regression coefficient (r: –0.10 [–0.15 to –0.05]; $p < 0.01$) for liver fibrosis compared to those in the low-ISCED group.

Our results are in contrast with a recent study by Stroffolini et al. showing that NAFLD was more often observed in subjects with high education levels (6.8% vs. 3.7%; $p \leq 0.01$) [23,37]. In the study mentioned above multiple logistic regression analysis showed no association of low education level with NAFLD (OR 1.03; 95% CI 0.81–1.30). Furthermore, a low education level was associated with a higher level of cirrhosis (29.1% vs. 15.8%; $p \leq 0.01$) [23,37]. It has been argued that lower levels of knowledge and access to care worsen disease progression to cirrhosis, while the lack of association between NAFLD and education level is due to low levels of physical activity and unhealthy food consumption in all social classes, regardless of education level [23,37].

The difference in study outcomes between Stroffolini et al. and the current study may be attributed to the utilization of different study populations. Stroffolini et al. recruited patients from cohorts of individuals with chronic liver disease, which may have introduced referral bias. On the other hand, the current study utilized a population-based cohort with a high risk of developing liver disease in Austria. However, the results of both studies are complementary. Stroffolini et al. demonstrated that individuals with a lower education level had a higher risk of fibrosis and cirrhosis in a population with chronic liver disease, which trend was also observed in the findings of the current study [23,37].

The association between LSM and ISCED further supports the research question of the recent study, as the results reveal that a lower educational attainment was associated with a higher liver stiffness measurement. These findings are consistent with the results presented by Oztumer et al., who demonstrated a correlation between liver stiffness and socioeconomic deprivation [23,38].

One potential explanation for the association between educational status and NAFLD and liver fibrosis is that individuals with lower ISCED may have less access to healthcare and information about healthy lifestyles, leading to a higher risk of developing NAFLD [37–39]. Recent studies have shown that all countries and healthcare systems in Europe exhibit relative and absolute educational inequalities [23,40]. Health care has been shown to play a very important role in the societal distribution of health, disease and death [23,41]. Hence, the health care system has an important role in balancing social positions [23,40]. However, even in high-income countries with publicly funded health care systems, unequal opportunity in terms of access to health care exists [23,39]. It has been argued that the unequal use of health services by distinct socioeconomic groups is a significant determining factor [23,39]. Primary health care is more often used by patients with lower SES, while significantly more professional contacts are reported in more highly educated groups [23,40]. It is believed that patients with lower education levels are less able to navigate within the complex health care system and often lack the numerical and linguistic skills to implement recommendations from doctors and nurses [23,39,40]. Furthermore, SES influences patients' dietary habits and access to high-quality nutrition [23,42]. A low SES is associated with a sedentary lifestyle, lower educational standards, differential access to greenspace, and obesity, indicating a poorer health status with a high impact of comorbidities [23,43].

Considering that participants with low SES more often face metabolic comorbidities NAFLD together with socioeconomic disadvantages and poor connections to the healthcare system, NAFLD-induced hepatocellular carcinoma should be given greater attention. Recent studies have shown that the most common underlying risk factor for HCC is NAFLD, followed by diabetes and hepatitis C virus (HCV) infection, representing 59%, 36% and 22% of all underlying causes of HCC, respectively [23,35,36]. It must be mentioned that in NAFLD compared to other liver diseases such as HCV or alcoholic liver disease, recent research has shown that HCC can develop even in a non-cirrhotic liver [23,44,45]. Further risk factors for developing HCC in non-cirrhotic NAFLD have shown to be older age, male gender and Hispanic ethnicity [23,46]. Studies have shown that obesity and T2D are additional risk factors for HCC [23,47]. Moreover, lifestyle behaviours related to low SES, such as smoking, seem to be implicated in NAFLD-associated HCC [23,48,49]. Finally, the development of HCC in patients with hepatitis B virus or HCV infection is believed to be further promoted by NAFLD itself [23,50]. In our opinion, HCC (hepatocellular carcinoma) will become a major public health issue for patients with NAFLD (nonalcoholic fatty liver disease), especially those with low socioeconomic status (SES) who face challenges in accessing healthcare. Thus, it is crucial to take into account the level of education of a population when examining the development of liver steatosis and its progression to fibrosis, cirrhosis, and HCC in epidemiological data. Further research is necessary to establish causality and raise awareness about the unequal access to preventive health care that results from low SES. Currently, there is no pharmaceutical treatment for NAFLD, so it is imperative to provide health education and promote lifestyle changes to patients with lower levels of education.

This study focused on educational status a surrogate marker for SES because of different reasons. Recent research has shown that it is a better marker for socioeconomic status (SES) than income due to several reasons [15–17]. While income has limitations in capturing an individual's social and economic standing, educational status provides a comprehensive view of SES [16]. Educational status remains stable over time, reflecting long-term achievement, unlike income, which can fluctuate [15–17]. Education is closely linked to social mobility, offering increased opportunities and better health literacy [23,39]. Moreover, educational attainment is influenced by upbringing and social capital, incorporating the impact of family background [51]. Overall, education level is a valuable marker for understanding socioeconomic disparities and designing targeted interventions [17]. In the context of NAFLD, using education level as a surrogate marker for SES allows for specific investigation and identification of modifiable risk factors. Additionally, education level enables direct comparisons across different populations, unaffected by cultural or regional variations in occupation or income. However, we recognize that people with varying educational backgrounds may have other differences, such as their level of health literacy, that are not directly measured. Nevertheless, we consider the use of educational status as a valuable tool for categorizing patients because it is a relatively simple and accessible marker that captures various aspects of their socioeconomic situation.

Nevertheless, we have to acknowledge some limitations. As a cross-sectional study, data of the current study are collected at a single point in time, and therefore, it is impossible to determine whether NAFLD caused a lower education level or vice versa. Therefore, we are not able to establish a cause-and-effect relationship. Other potential confounding factors may also be present, such as lifestyle choices, genetics, and environmental factors, which may affect both NAFLD and education level. Furthermore, we have to acknowledged limitations in conducting multivariate analysis and reporting of outcomes of this etiological modeling [23,26]. Incorporating Metabolic syndrome in the model may have introduced the risk of overfitting, potentially impacting the model's ability to generalize effectively. Nevertheless, given the

substantial effect size and the large sample size observed in our study, we maintain the validity of hypothesis generation. Robust findings of this study support the exploration of potential relationships. The ISCED categories provide comparability between countries, but national differences in surveying, coding and organization of the education system have not yet been considered. Regarding NAFLD diagnosis, participants did not undergo liver biopsies, which is another limitation, although biopsies should only be performed in those with progressive liver disease or unclear disease genesis [23,52]. Furthermore, we were not able to collect data for other aetiologias of chronic liver disease such as autoimmune disease, medication-induced liver disease or other factors [23,53,54]. However, we believe that the assumption that NAFLD is by far the most common hepatological disease is well-founded. Even if rarer liver diseases were underdiagnosed in this cohort, this would presumably have no statistical impact on the results.

The strength of this study is that it has large number of participants (n = 8727) from a high-risk population-based cohort. To accurately predict the presence of NAFLD, this study utilized an FLI score threshold of greater than 60, which has been proven by previous research. [23,55] Moreover, the FLI and FIB-4 scores are widely recognized as effective screening tools for liver fibrosis [23,52,56]. Importantly, subgroup analysis provided LSM data, the non-invasive gold standard for detecting liver fibrosis, resulting in a comprehensive and thorough examination of liver health [22,23]. Of particular significance, this study stands out for its inclusion of a representative sample of the general population, providing insights into liver disease beyond just high-risk groups. Additionally, the study's broad range of baseline features facilitated a comprehensive examination of a variety of covariates through the use of multivariable regression models. All in all, this study is one of the largest population-based studies in the field and represents a significant contribution to our understanding of liver health. Therefore, this study holds great importance for multiple reasons. NAFLD is a rapidly growing health concern globally and identifying risk factors for its development is critical to its effective prevention and management [1,2,23]. Socioeconomic status, including education level, has been shown to influence a range of health outcomes, and determining its link with NAFLD can identify vulnerable populations and help inform targeted interventions. [8–10,23] Although the association between education level and NAFLD has been investigated in several studies, there is limited research on this topic in population. Thus, this study contributes valuable information to the existing literature and provides new insights into the relationship between education level and NAFLD. The study's methodology, incorporating validated surrogate markers for NAFLD and fibrosis, and a large sample size, reinforces the study's findings and strengthens the reliability of its conclusions.

4.1. Conclusion

This study reveals a strong association between educational status and NAFLD risk. The low education group had a significantly higher NAFLD prevalence (40%) compared to the high education group (23%, $p<0.01$). Individuals in the intermediate and high ISCED group showed a substantial reduction in liver steatosis risk, even after accounting for potential confounding factors. A low educational status is identified as a major risk factor for NAFLD. This findings underscore the importance of addressing socioeconomic factors in NAFLD prevention and management, necessitating a comprehensive approach for equal healthcare and education access.

Funding

The study was financially supported the County of Salzburg, the Salzburger Landeskliniken (SALK, the Health Care Provider of the University Hospitals Landeskrankenhaus and Christian Doppler Klinik), the Paracelsus Medical University Salzburg, the Austrian Health Insurance (Österreichische Gesundheitskasse- ÖGK) and by unrestricted grants from Bayer, AstraZeneca, Sanofi-Aventis, Boehringer-Ingelheim.

Institutional review board statement

The study was conducted in accordance with the Dec-laration of Helsinki. The study has been approved by the local ethics committee number: 415- E/1521/6–2012.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

CRediT authorship contribution statement

Florian Koutny: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Elmar Aigner:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision. **Christian Datz:** Writing – review & editing. **Sophie Gensluckner:** Writing – review & editing, Writing – review & editing. **Andreas Maieron:** Conceptualization, Writing – review & editing, Supervision. **Andrea Mega:** Writing – review & editing. **Bernhard Iglseder:** Writing – review & editing. **Patrick Langthaler:** Writing – review & editing. **Vanessa Frey:** Writing – review & editing. **Bernhard Paulweber:** Writing – review & editing. **Eugen Trinka:** Writing – review & editing. **Bernhard Wernly:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

E.T. has received personal fees from Arvelle Therapeutics, Inc., Argenx, Bial, Biogen, Biocodex, Böhringer Ingelheim, Eisai, Epilog, Everpharma, GlaxoSmithKline, GW Pharma, Jazz Pharmaceuticals, LivaNova PLC, Marinus Pharmaceuticals, Inc., Medtronic, NewBridge Pharmaceuticals, Novartis, Sandoz, Sanofi, Sunovion Pharmaceuticals, Inc., Takeda, UCB Pharma, and Xenon; grants from Austrian Science Fund (FWF), Bayer, Biogen, Eisai, European Union, GlaxoSmithKline, Novartis, Österreichische Nationalbank, Red Bull, and UCB Pharma; He is CEO of NeuroConsult GmbH.; and has been a trial investigator for Eisai, GlaxoSmithKline, Marinus, Pfizer, and UCB Pharma; none COI related to the study. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results".

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request. The data are not publicly available due to restrictions, which apply to the availability of these data, which were used under license for this study. Data are available with permission from LIFE Child, Leipzig and the Leipzig Childhood Obesity Consortium.

Acknowledgments

We would like to thank all initiators of the Paracelsus 10,000 Study. The authors thank all contributors of the study and all staff who supported the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.07.039.

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