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ORIGINAL

Influence of sociodemographic variables and tobacco consumption on the risk of nonalcoholic fatty liver disease and liver fibrosis

Influencia de las variables sociodemográficas y del consumo de tabaco en el riesgo de padecer hígado graso no alcohólico y fibrosis hepática

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is the leading cause of liver disease in the Western world. Although it is normal to have a certain amount of fat in the liver, when it exceeds 10% it becomes a health problem. It is not usually a serious disease, unless it is accompanied by steatohepatitis (inflammation of the liver caused by the presence of fat), which can develop into cirrhosis and/or liver cancer.
Methods: A descriptive and cross-sectional study was carried out in 9,550 users of the Scottish National Health System in which the influence of sociodemographic variables such as age, sex and educational level and tobacco consumption on the prevalence of non-alcoholic fatty liver disease and liver fibrosis determined with different scales was assessed.
Results: The prevalence of high risk of NAFLD and liver fibrosis determined by risk scales is influenced by sex (more prevalent in men), age (increasing with age), educational level (higher prevalence in people with less education) and tobacco use (somewhat more prevalent in smokers, although only with the hepatic steatosis index).
Conclusions: The high-risk values in the NAFLD and hepatic fibrosis scales are influenced by sociodemographic variables and only in some cases by tobacco consumption.

Keywords: Fatty liver, liver fibrosis, tobacco.

Resumen

Introducción: El hígado graso no alcohólico (NAFLD) es la principal causa de enfermedad hepática en el mundo occidental. Aunque es normal tener una cantidad determinada de grasa en el hígado, cuando ésta supera el 10% se convierte en un problema de salud. No suele ser una enfermedad grave, a no ser que se acompañe de esteatohepatitis (inflamación del hígado causado por la presencia de grasa), lo que puede evolucionar en cirrosis y/o cáncer hepático.
Material y métodos: Se realizó un estudio descriptivo y transversal en 9,550 usuarios del Sistema Nacional de Salud de Escocia en los que se valoró la influencia de variables sociodemográficas como edad, sexo y nivel de estudios y, el consumo de tabaco en la prevalencia de Hígado graso no alcohólico y fibrosis hepática determinados con diferentes escalas.
Resultados: La prevalencia de alto riesgo de NAFLD y fibrosis hepática determinada mediante escalas de riesgo se ve influenciada por el sexo (más prevalente en hombres), edad (va incrementándose con la edad), nivel de estudios (mayor prevalencia en las personas con menores estudios) y consumo de tabaco (algo más prevalente en los fumadores aunque sólo con el hepatic steatosis index).
Conclusiones: Los valores de alto riesgo en las escalas de NAFLD y fibrosis hepática se ven influidos por las variables sociodemográficas y solo en algunos casos por el consumo de tabaco.

Palabras clave: Hígado graso, fibrosis hepática, tabaco.

Introduction

The main and defining characteristic of non-alcoholic fatty liver disease (NAFLD) is the accumulation of free fatty acids and triglycerides in the hepatocytes, specifically in the cytoplasm, mainly in the form of large fat vacuoles, in individuals who do not consume alcohol excessively (≤ 3 standard drinking unit/day in men and ≤ 2 standard drinking unit/day in women) and do not present other liver diseases[1]. Although in most cases it follows a benign course, a small percentage of patients may develop non-alcoholic steatohepatitis (NASH), characterized by the appearance of hydropic degeneration of the hepatocytes and lobular inflammation with or without perisinusoidal fibrosis, which can progress to cirrhosis and hepatocellular carcinoma, leading to death due to liver disease[2].

NAFLD is currently considered the leading cause of liver disease in the Western world, with an estimated prevalence of 20-30% according to the criteria used in different studies[3-5].

The causal factors of NAFLD can be divided into primary factors, which are the most important, and are related to the different components of the metabolic syndrome such as obesity, type 2 diabetes and dyslipidemia[6-9]. NAFLD could be considered the hepatic component of the metabolic syndrome. Insulin resistance would be the determining alteration of steatosis and this in turn would be responsible for inflammatory disorders (IL-6, TNFα), oxidative stress, mitochondrial dysfunction, NASH and fibrosis[10-14]. Secondary factors are less frequent, and are related to the consumption of drugs (corticosteroids, estrogens, amiodarone, tamoxifen), bariatric surgery, parenteral nutrition, congenital metabolic diseases and other toxins[6,7]. In clinical practice, many patients with NAFLD present obesity, type 2 diabetes or dyslipidemia as a causal factor, and the association of various factors is frequent.

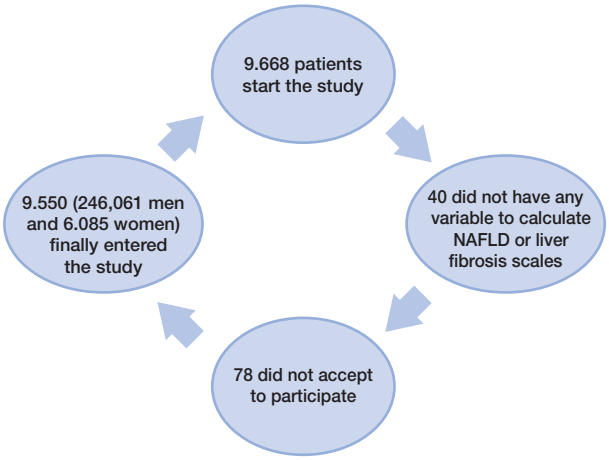
Blood tests (elevated liver enzymes ALT and AST), diagnostic imaging (ultrasound, CT and MRI) and even liver biopsy are used to diagnose NAFLD. There are also several scales that assess the risk of NAFLD as we will see below.

The aim of this work is to know how different sociodemographic variables such as age, sex, educational level and tobacco consumption affect the risk of NAFLD and liver fibrosis.

Methods

Retrospective, cross-sectional study in a sample of 9668 users of the *National Health Service* between January 2018 and June 2020. 78 did not agree to participate in the study and 40 lacked some of the variables necessary to calculate the fatty liver or liver fibrosis scales. The total number of participants who entered the study was 9550. (see Flow chart in **figure 1**).

Figure 1: Participant flow chart.



Inclusion criteria

- Age between 18 and 70 years.
- Agree to participate in the study by giving up data for epidemiological purposes.

Sociodemographic variables such as age and sex, level of education (primary, secondary and university) and tobacco consumption were collected, being considered smokers when they had regularly consumed at least 1 cigarette/day (or its equivalent in other types of consumption) in the last month, or had quit less than 1 year ago.

Fatty liver and hepatic fibrosis risk scales

- Lipid accumulation product (LAP)[15]
- Men: (waist circumference (cm) – 65) x (trigycerides (mMol)).
- Women: (waist circumference (cm) – 58) x (trigycerides (mMol))

- Fatty liver index (FLI)[16]

$$FLI = (e^{0.953*\log_e(\text{triglycerides}) + 0.139*BMI + 0.718*\log_e(GGT) + 0.053*\text{waist circumference} - 15.745}) / (1 + e^{0.953*\log_e(\text{triglycerides}) + 0.139*BMI + 0.718*\log_e(GGT) + 0.053*\text{waist circumference} - 15.745}) \times 100$$

A person is considered to be at high risk when the FLI value is equal to or greater than 60

- Hepatic steatosis index (HSI)[17]
HSI = 8 x ALT/AST + BMI (+ 2 if type 2 diabetes yes, + 2 if female)

- Zhejian University index (ZJU)[18]
BMI + FPG mmol L + TG mmol L+ 3 ALT/AST + 2 if female

- Fatty liver disease index (FLD)[19]
BMI + TG + 3 × (ALT/AST) + 2 × Hyperglycemia (presence= 1; absence = 0)

Values <28.0 or >37.0 excluded the possibility of NAFLD

- Framingham steatosis index[20]
FSI = −7.981 + 0.011x age − 0.146 x sex (female = 1, male = 0) + 0.173 x BMI + 0.007 x TG + 0.593 x hypertension (yes = 1, no = 0) + 0.789 x diabetes (yes = 1, no = 0) + 1.1 x ALT/AST ratio ≥ 1.33 (yes = 1, no = 0).

- Bard scoring system (BSS)[21]
BMI ≥ 28 = 1 point, AST/ALT ≥ 0.8 = 2 points, type 2 diabetes mellitus = 1 point.
Cut off for high risk 2 points

Statistical analysis

A descriptive analysis of the categorical variables was performed and the frequency and distribution of the responses were calculated for each of them. The mean and standard deviation were calculated for quantitative variables, and the percentage for qualitative variables. A bivariate association analysis was performed using the χ^2 test (with a correction with Fisher's exact test, when conditions required it) and a Student's t test for independent samples. For the multivariate analysis, binary logistic regression was used with the Wald method, with calculation of the Odds ratio, and the Hosmer-Lemeshow goodness-of-fit test was performed.

Statistical analysis was performed with the SPSS 27.0 program, and a p value of <0.05 was considered statistically significant.

Ethical considerations and aspects

The study was approved by the Clinical Research Ethics Committee. The procedures were performed following the ethical standards of the institutional research committee and with the 2013 Declaration of Helsinki. All patients signed written informed consent documents before participating in the study.

Results

The mean age of the patients included in our study was slightly over 47 years. Most of them had primary education. Women smoked more than men. The clinical and analytical variables are more unfavorable in men, the differences being statistically significant in most cases as can be seen in **table I**.

The mean values of all fatty liver and liver fibrosis scales analyzed in this study are higher in men. An increase in the values of all scales is observed as the age of the patients increases. People with a university education are those with the most favorable values in all scales. Smokers have lower values than non-smokers. In all cases, the differences observed were statistically significant. The complete data can be found in **table II**.

Table I: Sociodemographic, anthropometric, clinical and analytical characteristics of the sample.

	Men n=6085 Mean (SD)	Women n=3465 Mean (SD)	Total n=9550 Mean (SD)	p-value
Age (years)	47.55 (8.32)	46,97 (7.92)	47.34 (8.19)	0.001
Height (cm)	174.94 (6.65)	161.90 (6.19)	170.21 (9.02)	<0.0001
Weight (kg)	83.61 (14.52)	67.47 (13.07)	77.75 (16.02)	<0.0001
Body mass index (kg/m²)	27.29 (4.31)	25.75 (4.85)	26.73 (4.58)	<0.0001
Waist circumference (cm)	84.84 (7.93)	73.25 (8.52)	80.63 (9.87)	<0.0001
Waist to height ratio	0.49 (0.04)	0.45 (0.05)	0.47 (0.05)	<0.0001
Systolic blood pressure (mmHg)	128.07 (15.93)	117.69 (16.33)	124.30 (16.83)	<0.0001
Diastolic blood pressure (mmHg)	78.83 (11.05)	73.22 (10.85)	76.79 (11.30)	<0.0001
Total cholesterol (mg/dL)	201.90 (36.33)	199.90 (34.13)	201.17 (35.55)	0.008
HDL-cholesterol (mg/dL)	52.61 (8.98)	57.77 (9.75)	54.48 (9.60)	<0.0001
LDL-cholesterol (mg/dL)	122.97 (34.38)	122.79 (32.77)	122.90 (33.80)	0.809
Triglycerides (mg/dL)	133.18 (77.00)	96.93 (48.27)	120.03 (70.19)	<0.0001
Glucose (mg/dL)	95.05 (24.19)	88.47 (17.98)	92.66 (22.36)	<0.0001
ALT (U/L)	28.79 (14.65)	19.40 (9.51)	25.39 (13.78)	<0.0001
AST (U/L)	24.12 (9.52)	18.54 (7.00)	22.10 (9.09)	<0.0001
GGT (U/L)	34.22 (26.38)	20.11 (15.00)	29.10 (23.89)	<0.0001
	Percentage	**Percentage**	**Percentage**	**p-value**
18-39 years	18.32	17.63	18.07	<0.0001
40-49 years	39.43	46.24	41.90	
50-69 years	42.25	36.13	40.03	
Primary school	69.09	51.95	62.87	<0.0001
Secondary school	21.74	37.23	27.36	
University	9.17	10.82	9.77	
Non-smokers	72.62	68.69	71.19	<0.0001
Smokers	27.38	31.31	28.81	

The prevalence of high-risk values of all the scales, both of nonalcoholic fatty liver disease and liver fibrosis, is much higher in men. An increase in prevalence is also observed parallel to the increase in age. As with the mean values, the most disadvantaged group in the prevalence of high-risk scales is the group with the lowest level of education. Non-smokers have a higher prevalence in all the high-risk scales. In all cases the differences show statistical significance. The complete data can be found in **table III**.

In the multivariate analysis using binary logistic regression, age 50 years or older, male sex, non-university education, and tobacco consumption were established as covariates. Age over 50 years and male sex were the variables that most increased the risk of presenting nonalcoholic fatty liver disease or liver fibrosis. Tobacco consumption increases the risk exclusively with hepatic steatosis index. All the data from the multivariate analysis are presented in **table IV**.

Discussion

Male sex is the variable that most increases the risk of presenting NAFLD in all the scales assessed in this study. Age is another variable that also increases the risk in all the scales. Low socioeconomic level increases the risk of NAFLD in all except the Fatty liver disease index. Tobacco consumption only influences NAFLD when assessed with the hepatic steatosis index.

The increase in the prevalence of NAFLD with age obtained in our work has also been observed in other studies consulted; thus, in 550 Japanese studies[22] it was seen that both NAFLD and liver fibrosis diagnosed

Table II: Mean values of different fatty liver and liver fibrosis scales according to sociodemographic variables and tobacco consumption.

	n	FLI Mean (SD)	HSI Mean (SD)	ZJU Mean (SD)	FLD Mean (SD)	FSI Mean (SD)	LAP Mean (SD)	BSS Mean (SD)
Men	6085	39.74 (24.93)	37.43 (6.56)	37.77 (5.56)	32.59 (5.18)	0.23 (0.19)	31.16 (25.41)	1.38 (1.06)
Women	3465	18.35 (20.68)	36.52 (6.27)	36.99 (5.62)	30.11 (5.35)	0.15 (0.16)	17.86 (16.58)	0.82 (0.89)
18-39 years	1726	29.40 (26.56)	36.80 (6.83)	36.90 (5.81)	31.26 (5.72)	0.16 (0.17)	24.77 (24.26)	0.71 (0.89)
40-49 years	4001	29.73 (25.09)	36.82 (6.26)	37.08 (5.29)	31.31 (5.22)	0.18 (0.17)	24.64 (22.69)	0.74 (0.88)
50-70 years	3823	35.47 (25.37)	37.51 (6.45)	38.17 (5.70)	32.24 (5.30)	0.24 (0.20)	28.82 (23.79)	1.84 (0.88)
Primary school	6004	34.47 (26.09)	37.37 (6.62)	37.87 (5.82)	32.15 (5.50)	0.22 (0.19)	28.03 (24.23)	1.26 (1.03)
Secondary school	2613	27.35 (24.09)	36.73 (6.26)	36.88 (5.16)	30.92 (5.09)	0.17 (0.16)	23.32 (22.07)	1.01 (1.00)
University	933	28.87 (24.72)	36.33 (5.94)	36.72 (5.06)	30.87 (5.00)	0.18 (0.17)	23.90 (21.44)	1.08 (1.06)
Non-smokers	6799	32.50 (25.69)	37.16 (6.40)	37.56 (5.57)	31.78 (5.34)	0.20 (0.19)	26.79 (23.69)	1.19 (1.04)
Smokers	2751	30.67 (25.45)	36.94 (6.64)	37.30 (5.65)	31.46 (5.46)	0.19 (0.18)	25.20 (22.99)	1.13 (1.03)

FLI: Fatty liver index, HSI: Hepatic steatosis index, ZJU: Zhejian University index, FLD: Fatty liver disease, FSI: Framingham steatosis index, LAP: Lipid accumulation producto, BSS: Bard scoring system.
In all cases the differences are statistically significant.

Table III: Prevalence of high risk of different fatty liver and liver fibrosis scales according to sociodemographic variables and tobacco consumption.

	n	FLI high risk Percentage	HSI high risk Percentage	ZJU high risk Percentage	FLD high risk Percentage	LAP high risk Percentage	BSS high risk Percentage
Men	6085	22.96	54.49	42.55	65.06	36.11	41.59
Women	3465	7.04	47.22	36.25	48.66	22.42	20.81
18-39 years	1726	15.16	42.35	34.59	53.94	27.11	18.13
40-49 years	4001	15.30	49.41	38.17	58.14	27.94	18.87
50-70 years	3823	19.62	56.08	45.02	62.46	36.31	57.13
Primary school	6004	19.47	53.51	42.85	60.03	33.73	36.91
Secondary school	2613	12.94	49.67	35,82	57.90	27.02	28.93
University	933	14.36	47.37	36.01	56.59	26.05	30.01
Non-smokers	6799	17.59	52.67	40.67	59.76	31.73	34.53
Smokers	2751	16,18	49,84	39.26	57.51	29.70	32.86

FLI: Fatty liver index, HSI: Hepatic steatosis index, ZJU: Zhejian University index, FLD: Fatty liver disease, FSI: Framingham steatosis index, LAP: Lipid accumulation producto, BSS: Bard scoring system.
In all cases the differences are statistically significant.

Table IV: Multivariate binary logistic regression analysis.

	50-70 years OR 95% CI	p-value	Male OR 95% CI	p-value	Non university OR 95% CI	p-value	Smokers OR 95% CI	p-value
FLI high risk	1.26 (1.13-1.40)	<0.0001	3.88 (3.36-4.48)	<0.0001	1.23 (1.01-1.49)	0.042		ns
HSI high risk	1.31 (1.20-1.43)	<0.0001	1.31 (1.20-1.43)	<0.0001	1.21 (1.06-1.39)	0.006	1.10 (1.01-1.19)	0.026
ZJU high risk	1.37 (1.26-1.49)	<0.0001	1.28 (1.17-1.39)	<0.0001	1.22 (1.06-1.40)	0.007		ns
FLD high risk	1.22 (1.12-1.33)	<0.0001	1.94 (1.79-2.12)	<0.0001		ns		ns
LAP high risk	1.45 (1.33-1.58)	<0.0001	1.91 (1.74-2.11)	<0.0001	1.30 (1.12-1.52)	0.001		ns
BSS high risk	6.01 (5.46-6.61)	<0.0001	2.86 (2.57-3.17)	<0.0001	1.29 (1.10-1.53)	0.002		ns

by biopsy were more frequent in older persons, which led to the conclusion that age is strongly associated with the development and progression of NAFLD. Something similar was observed in a study of 5[22] Indian diabetics[23].

In our research, males have a higher risk of developing NAFLD and hepatic fibrosis, these data are similar to those found in the Chinese population[24] where the OR were 3.48 (similar to those found by us with FLI). In this study the diagnosis was made with ultrasound. However, other authors have found a higher prevalence in women[23] and others have found no differences between the sexes[25].

Our data indicate that the prevalence of NAFLD is higher in people with lower socioeconomic status, and these data coincide with those found by other authors. In a study carried out in a Chinese population[26] it was found that people with a low socioeconomic level were 2.19 times more at risk than those with a higher standard of living. An investigation in 5272 Koreans[27] assessing the relationship between social status and muscle strength with the occurrence of NAFLD showed that both low socioeconomic status and decreased muscle strength were independently and synergistically associated with an increased risk of NAFLD in older persons. One study compared the prevalence of NAFLD in 21 countries[28] with different economic status and concluded that prevalence correlated positively with the per capita income of individuals, such that countries with higher economic status tend to have a higher prevalence of NAFLD. A study in young people under 21 years of age showed that NAFLD appeared earlier in the more economically disadvantaged group but there was no difference in severity[29].

We have only found a relationship between smoking and NAFLD when assessed with HSI, finding an increased prevalence among smokers. Two Korean studies also found a positive relationship, one in almost 200,000 people where current smoking levels, pack-years and urinary cotinine levels were positively associated with the risk of developing NAFLD, suggesting that smoking contributed to the development of NAFLD[30]. The other Korean study in 160 862 persons[31] with similar methodology concluded that cotinine-verified current smoking and self-reported current smoking were independent risk factors for NAFLD. A study in 8580 Chinese[32] over 40 years of age assessed the effect of passive and active smoking on NAFLD determined by ultrasound and liver enzymes and observed that passive smoking and heavy active smoking were associated with increased prevalence.

The strengths of this study include the large sample size, almost 10,000 people, and the large number of scales that evaluate fatty liver and liver fibrosis, a total of 7 scales. As limitations we would highlight the lack of objective diagnostic methods for the diagnosis of NAFLD.

Conflicts of interest

The authors declare no conflicts of interest.

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