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ORIGINAL

Influence of tobacco consumption on the values of different insulin resistance risk scales and non-alcoholic fatty liver disease and hepatic fibrosis scales in 418,343 spanish people

Influencia del consumo de tabaco en los valores de diferentes escalas de riesgo de resistencia a la insulina y de enfermedad de hígado graso no alcohólico y fibrosis hepática en 418.343 españoles

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Summary

Introduction and objectives: Insulin resistance (IR) and non-alcoholic fatty liver disease (NAFLD) are two very frequent pathologies that are responsible for the appearance of different pathological conditions. A multitude of factors are involved in the genesis of both processes. The aim of this study was to assess the influence of various sociodemographic factors such as age, sex, social class, and tobacco consumption on IR and NAFLD.
Methodology: A descriptive, cross-sectional study carried out in 418343 Spanish workers in which the relationship between sociodemographic variables and tobacco consumption with risk scales for IR, NAFLD, and liver fibrosis was assessed.
Results: All the variables analyzed influence the appearance of IR, NAFLD, and liver fibrosis, especially age and sex. Being male, of advanced age, belonging to social class III, and being a smoker increased the risk of IR, NAFLD, and liver fibrosis.
Conclusions: All the sociodemographic variables analyzed, and tobacco use influence the occurrence of IR, NAFLD, and liver fibrosis.

Key words: Insulin resistance, nonalcoholic fatty liver disease, liver fibrosis, tobacco.

Resumen

Introducción y objetivos: La resistencia a la insulina (RI) y la enfermedad del hígado graso no alcohólico (EHGNA) son dos patologías muy frecuentes que son responsables de la aparición de diferentes cuadros patológicos. En la génesis de ambos procesos intervienen multitud de factores. El objetivo de este estudio es valorar la influencia de diversos factores sociodemográficos como la edad, el sexo o la clase social y el consumo de tabaco en la RI y en la EHGNA.
Metodología: Estudio descriptivo y transversal realizado en 418343 trabajadores españoles en el que se valora la relación entre variables sociodemográficas y consumo de tabaco con escalas de riesgo de RI, EHGNA y fibrosis hepática.
Resultados: Todas las variables analizadas influyen en la aparición de RI, EHGNA y fibrosis hepática, especialmente la edad y el sexo. Ser varón, de edad avanzada, pertenecer a la clase social III y ser fumador incrementan el riesgo de RI, EHGNA y fibrosis hepática.
Conclusiones: Todas las variables sociodemográficas analizadas y el consumo de tabaco influyen en la aparición de RI, EHGNA y fibrosis hepática.

Palabras clave: Resistencia a la insulina, enfermedad del hígado graso no alcohólico, fibrosis hepática, tabaco.

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Introduction

When there is excess blood glucose, cells are unable to absorb and utilize blood sugar for energy production, resulting in insulin resistance (IR)[1]. This situation increases the risk of developing prediabetes[2] and ultimately type 2[3] diabetes. Diabetes is less likely to develop and blood glucose will remain within a healthy range if the pancreas can produce enough insulin to overcome the low absorption rate[4].

The liver disease that affects people who drink little or no alcohol is known as non-alcoholic fatty liver disease (NAFLD). As the name implies, the main feature of NAFLD is the excessive accumulation of fat in liver cells.

NAFLD is increasing in frequency worldwide, especially in Western countries[5]. Approximately one-quarter of the U.S. population has this form of chronic liver disease[6].

Some patients with NAFLD may develop non-alcoholic steatohepatitis[7], an aggressive form of fatty liver disease characterized by inflammation of the liver that can progress to advanced scarring (cirrhosis)[8] and liver failure[9]. Excessive alcohol consumption causes the same damage.

The aim of this study was to determine how different sociodemographic variables such as age, sex, socioeconomic level, and tobacco consumption affect the prevalence of insulin resistance, NAFLD, and liver fibrosis in a large group of Spanish workers.

Methods

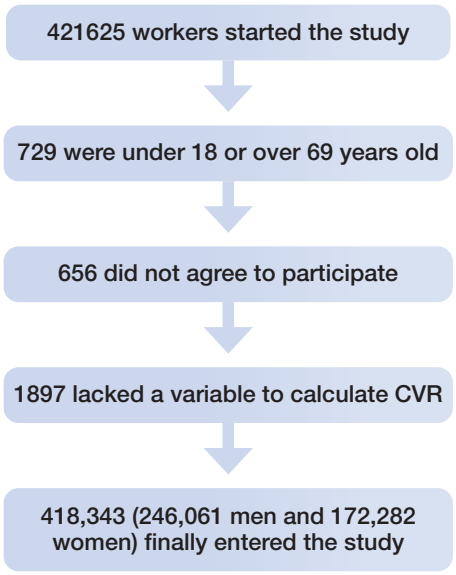
A descriptive, cross-sectional study was conducted in 418,343 Spanish workers from different regions and productive sectors between January 2017 and December 2019. Individuals were selected from among those who underwent regular health examinations in the different participating companies.

The following were the requirements to participate in the study: being between 18 and 69 years old, working for a company involved in the study, not being temporarily incapacitated, and signing the informed consent to participate in the study and use their data for epidemiological purposes.

Figure 1 shows the flow diagram of the study participants.

Table I shows the characteristics of the population, with all the anthropometric, clinical, and analytical variables showing higher or less favorable values in men. The most frequent age was between 30 and 49 years. Most of the employees belonged to social class III and had only a primary education. Approximately every third person in the study smoked.

Figure 1: Flowchart.



Measurement and data collection

Anthropometric measurements (height, weight, and waist circumference) were taken clinically and analytically by the health professionals of the companies participating in the study after standardization of the measurement techniques.

Weight and height were measured with a SECA model 700 measuring scale. A SECA tape measure was used while the person was standing, feet together, trunk erect, and abdomen relaxed to measure waist circumference. The tape was placed parallel to the floor at the level of the end floating rib.

The person's blood pressure was measured while seated, after a 10-minute rest, with a calibrated OMRON M3 automatic sphygmomanometer. Measurements were taken three times with a period of one minute between them and the mean of the three was recorded. Analytical parameters were obtained after 12 hours of fasting. Total cholesterol, triglycerides, and blood glucose were obtained using automated enzymatic methods. Meanwhile, a precipitation process with dextran sulfate-MgCl2 was used to obtain HDL-c. The Friedewald formula was used to calculate LDL-c indirectly. Each analysis parameter was expressed in milligrams per deciliter.

$$LDL = \text{total cholesterol} - HDL - \text{triglycerides}/5$$

The following insulin resistance risk scales were calculated:

- Triglycerides/HDL-c. A risk ratio greater than 2.4 is considered dangerous[10].
- Triglyceride Glucose Index (TyG). This can be obtained using the following formula: Ln (triglycerides [mg/dL] × glucose [mg/dL]/2). Values above 8.8[11] are considered high.

Derived from the TyG index, there are other indicators that also assess the risk of IR, such as TyG-BMI[12], TyG-waist[13], and TyG-WtHR[14].

- Metabolic score for insulin resistance (METS-IR)[15].
METS-IR = Ln(2 × glucose) + triglycerides × BMI)/ (Ln(HDL-c). High values are defined as 50 and above.

The NAFLD risk scales employed in this study were:
- Fatty Liver Index (FLI)[16].

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

Low risk below 30, moderate risk between 30-59, and high risk from 60 onwards.

- Hepatic steatosis index (HSI)[17]
8 × AST/ALT + BMI + 2 if diabetes + 2 if female.
Low risk <30, moderate 30-35.9 and high risk ≥ 36.

- Zhejiang University index (ZJU index)[18]
BMI + Blood glucose (mmol L) + Triglycerides (mmol L) +3 AST/ALT +2 if female.
Low risk < 32, moderate 32-37.9 high risk ≥ 38.

- Fatty liver disease index (FLD)[19]
BMI+ Triglycerides + 3 × (AST/ALT) +2 × Hyperglycemia (present=1; absent=0).
Low risk < 28, moderate 28-36,9 high risk ≥ 37.

- Lipid accumulation product (LAP)[20]
Men: (waist (cm) - 65) x (triglycerides (mMol)).
Women: (waist (cm) - 58) x (triglycerides (mMol)). High risk ≥ 42.7

BARD score[21] is calculated as the liver fibrosis risk scale.

If BMI ≥28 = 1 point, AST/ALT ≥ 0.8 = 2 points, diabetes = 1 point.

BARD score > 2 high risk of liver fibrosis.

Those who had smoked at least one cigarette a day (or its equivalent in other types of consumption) in the previous 30 days or who had quit smoking less than a year before were considered smokers.

The Spanish Society of Epidemiology establishes three categories of social classes according to profession and the proposal of the social determinants group[22]. Directors, managers, sportsmen and artists, university professionals and skilled self-employed workers belong to Class I. Unskilled self-employed workers and intermediate occupations belong to Class II. Unskilled workers make up Class III.

Statistical analysis

The frequency and distribution of categorical variables were calculated, and a descriptive analysis was performed. The mean and standard deviation of quantitative variables are calculated as the variables presented a normal distribution.

For independent samples, the Chi-squared test and Student's t-test were used. When circumstances required it, Fisher's exact statistic was corrected. To perform the multivariate analysis, multinomial logistic regression was used to calculate odds ratios and their 95% confidence intervals. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) Windows version 28.0 program, which had an accepted statistical significance level of 0.05.

Ethical considerations and/or aspects

The research team always undertook to comply with the standards of research ethics that govern health sciences, established both nationally and internationally in the Declaration of Helsinki, giving special importance to the anonymization of the participants and the confidentiality of the data obtained. The study was approved with indicator IB 4383/20 by the Ethics and Research Committee of the Balearic Islands (CEI-IB). As participation in the study was voluntary, participants gave both oral and written consent after receiving sufficient information regarding the nature of the study. To achieve this, they were given an information sheet with an explanation of the aim of the study, as well as an informed consent form.

The study data were identified using a code, and only the person responsible for the study can connect them to the participants. The identity of the participants will not be disclosed in the results of this study. The researchers will not disclose any information that identifies them. In any event, the research team is committed to complying with Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, ensuring that study participants have the right to access, rectify, cancel, and oppose the data collected.

Results

As shown in **table I**, more than 58% of the study participants were men. The average age was 40 years, with most people between 30 and 49 years of age. About 75% of the population belonged to social class III and about 33% smoked. The analytical and clinical variables were more advantageous for women.

Table II shows the mean values of the different risk scales for insulin resistance, NAFLD, and liver fibrosis according to smoking in both sexes. It can be observed that all these mean values were higher in the group of smokers in both men and women, with the differences found being statistically significant. In general, the mean values were higher in men.

Table III shows the prevalence of elevated values for all the risk scales (insulin resistance, NAFLD, and liver fibrosis), revealing the same trend seen for the mean values, i.e., greater prevalence among smokers and in general higher figures in men. All the differences observed were statistically significant.

Table IV shows the results of the multivariate analysis using multinomial logistic regression. The reference variables were female sex, aged under 30 years, social class I, and non-smokers. Odds ratios (OR) with 95% confidence intervals were calculated and it was found that all the sociodemographic variables analyzed, and tobacco consumption increased the risk of presenting high values in the different risk scales, for insulin resistance, NAFLD, and liver fibrosis. The highest OR values were found for age and sex. Tobacco consumption increased the risk, but only slightly.

Table I: Characteristics of the population.

	Women n=172.282 Mean (SD)	Men n=246.061 Mean (SD)	Total n=418.343 Mean (SD)	p-value
Age	39.6 (10.8)	40.6 (11.1)	40.2 (11.0)	<0.0001
Height	161.8 (6.5)	174.6 (7.0)	169.4 (9.3)	<0.0001
Weight	66.2 (14.0)	81.4 (14.7)	75.1 (16.2)	<0.0001
Waist	74.8 (10.6)	86.2 (11.1)	81.5 (12.2)	<0.0001
SBP	117.4 (15.7)	128.2 (15.5)	123.7 (16.5)	<0.0001
DBP	72.6 (10.4)	77.8 (11.0)	75.6 (11.0)	<0.0001
Cholesterol	190.6 (35.8)	192.6 (38.9)	191.8 (37.7)	<0.0001
HDL-c	56.8 (8.7)	50.3 (8.5)	53.0 (9.1)	<0.0001
LDL-c	116.1 (34.8)	118.0 (36.7)	117.2 (35.9)	<0.0001
Triglycerides	89.1 (46.2)	123.7 (86.4)	109.5 (74.6)	<0.0001
Glycemia	87.8 (15.1)	93.3 (21.3)	91.0 (19.2)	<0.0001
	%	%	%	p-value
18-29 years	20.7	18.8	19.6	<0.0001
30-39 years	29.7	27.6	28.4	
40-49 years	29.6	30.0	29.9	
50-59 years	16.8	19.7	18.5	
≥60 years	3.2	3.9	3.6	
Social class I	6.9	4.9	5.7	<0.0001
Social class II	23.4	14.9	18.4	
Social class III	69.7	80.3	75.9	
Non-smokers	67.2	66.6	66.9	<0.0001
Smokers	32.8	33.4	33.2	

Table II: Mean values of the insulin resistance, non-alcoholic fatty liver disease, and liver fibrosis scales according to smoking by sex.

	Men			Women		
	Non-smokers n=163920 Mean (SD)	Smokers n=82141 Mean (SD)	p-value	Non-smokers n=115727 Mean (SD)	Smokers n=56555 Mean (SD)	p-value
TG/HDL	2.6 (2.1)	2.7 (2.2)	<0.0001	1.6 (1.0)	1.7 (1.0)	0.01
TyG index	8.5 (0.6)	8.7 (0.6)	0.017	8.2 (0.5)	8.4 (0.5)	0.047
METS-IR	39.1 (8.6)	39.3 (8.5)	0.012	35.0 (8.4)	35.5 (8.4)	0.001
FLI	37.6 (27.5)	37.9 (27.5)	0.001	18.1 (21.8)	18.4 (21.8)	0.019
HSI	36.7 (6.9)	36.9 (6.7)	0.013	36.2 (6.8)	36.8(6.9)	0.001
ZJU	37.1 (5.7)	37.5 (5.7)	0.017	36.8 (6.1)	37.4 (6.2)	0.003
FLD	32.0 (5.3)	32.3 (5.4)	0.011	29.9 (5.9)	30.2 (5.9)	0.001
LAP	31.7 (32.9)	32.4 (33.7)	<0.0001	18.0 (18.4)	18.4 (18.2)	0.018
BARD	1.7 (1.1)	1.8 (1.1)	0.027	1.9 (1.0)	2.0 (1.0)	0.038

TG/HDL triglycerides/high density lipoproteins; TyG triglyceride/glucose index; METS-IR metabolic score for insulin resistance; FLI Fatty liver index; HSI hepatic steatosis index; ZJU Zhejiang university index; FLD fatty liver disease; LAP lipid accumulation product.

Table III: Prevalence of high values of insulin resistance and non-alcoholic fatty liver disease scales according to tobacco use by sex.

	Men			Women		
	Non-smokers n=163920 %	Smokers n=82141 %	p-value	Non-smokers n=115727 %	Smokers n=56555 %	p-value
High TG/HDL	25.0	25.3	0.001	17.8	18.2	0.018
High TyG index	27.3	27.6	0.017	12.4	12.7	0.011
High METS-IR	11.3	11.7	0.001	6.2	6.5	0.001
High FLI	24.1	24.5	0.001	7.7	7.9	0.012
High HSI	49.3	49.9	0.001	43.9	45.1	<0.0001
High ZJU	38.2	38.7	0.013	34.8	35.8	<0.0001
High FLD	60.9	61.5	<0.0001	44.5	44.9	0.013
High LAP	36.4	36.8	0.015	24.5	24.9	0.028
High BARD	65.1	65.3	0.010	77.0	77.5	0.001

TG/HDL triglycerides/high density lipoproteins; TyG triglyceride/glucose index; METS-IR metabolic score for insulin resistance; FLI Fatty liver index; HSI hepatic steatosis index; ZJU Zhejiang university index; FLD fatty liver disease; LAP lipid accumulation product.

Table IV: Multinomial logistic regression.

	High TG/HDL OR (95% CI)	High TyG OR (95% CI)	High METS-IR OR (95% CI)	High FLI OR (95% CI)	High HSI OR (95% CI)	High ZJU OR (95% CI)	High FLD OR (95% CI)	High LAP OR (95% CI)	High BARD OR (95% CI)
18-29 years	1	1	1	1	1	1	1	1	1
30-39 years	1.26 (1.21-1.30)	1.31 (1.27-1.36)	1.15 (1.10-1.21)	1.08 (1.05-1.12)	1.17 (1.07-1.27)	1.25 (1.15-1.36)	1.18 (1.08-1.29)	1.04 (1.00-1.07)	1.19 (1.08-1.32)
40-49 years	1.84 (1.78-1.91)	2.04 (1.97-2.11)	1.54 (1.47-1.61)	1.20 (1.15-1.26)	1.45 (1.33-1.57)	1.63 (1.50-1.77)	1.33 (1.22-1.45)	1.28 (1.24-1.33)	1.34 (1.21-1.48)
50-59 years	2.93 (2.83-3.04)	3.40 (3.28-3.53)	2.36 (2.25-2.48)	1.85 (1.77-1.93)	1.96 (1.80-2.13)	2.38 (2.18-2.58)	1.72 (1.58-1.88)	1.84 (1.77-1.90)	1.46 (1.33-1.61)
60-69 years	5.60 (5.38-5.83)	6.98 (6.69-7.27)	4.07 (3.86-4.30)	3.41 (3.24-3.58)	3.06 (2.80-3.34)	3.82 (3.49-4.17)	2.49 (2.28-2.73)	3.07 (2.96-3.18)	1.50 (1.36-1.65)
Female	1	1	1	1	1	1	1	1	1
Male	1.47 (1.45-1.50)	2.57 (2.53-2.62)	1.76 (1.72-1.80)	3.70 (3.62-3.78)	1.16 (1.13-1.20)	1.07 (1.03-1.10)	1.94 (1.89-2.00)	1.72 (1.70-1.74)	0.54 (0.53-0.56)
Social class I	1	1	1	1	1	1	1	1	1
Social class II	1.19 (1.17-1.22)	1.22 (1.19-1.24)	1.49 (1.44-1.54)	1.24 (1.19-1.30)	1.11 (1.07-1.16)	1.22 (1.17-1.27)	1.06 (1.03-1.10)	1.11 (1.09-1.13)	1.15 (1.10-1.21)
Social class III	1.39 (1.34-1.44)	1.42 (1.35-1.47)	1.78 (1.68-1.88)	1.26 (1.23-1.29)	1.37 (1.29-1.46)	1.51 (1.42-1.61)	1.07 (1.01-1.13)	1.26 (1.22-1.30)	1.13 (1.08-1.18)
Non-smokers	1	1	1	1	1	1	1	1	1
Smokers	1.03 (1.01-1.05)	1.03 (1.00-1.04)	1.02 (1.00-1.04)	1.06 (1.03-1.09)	1.02 (1.00-1.04)	1.11 (1.08-1.14)	1.07 (1.05-1.11)	1.01 (1.00-1.02)	1.02 (1.00-1.06)

Discussion

Our study shows an increase in the risk of presenting IR, NAFLD, and liver fibrosis in men, with increasing age, especially in people with a low socioeconomic level (social class III). Increased risk was also seen among smokers.

A study based on data from the National Health and Nutrition Examination Survey (NHANES) (2009-2018)[23] conducted in more than 12000 US adults showed that the prevalence of insulin resistance, using TyG for diagnosis, ranged from 13.9% to 22.5%, figures somewhat lower than those obtained in our sample. A meta-analysis performed in Southeast Asia[24] that included 12 studies and 2198 individuals between 2016-2021 estimated the prevalence of insulin resistance in that region at 44.3%, figures well above those obtained by us. Data from Spain[25] estimate that the prevalence of insulin resistance in men is 30%, while in women it is 20% to 22%. This figure is directly related to the increase in abdominal perimeter as an indicator of central obesity, affecting 50% of people with an abdominal perimeter greater than 100 cm. The overall prevalence of insulin resistance in the most developed countries has been estimated at 25-35%[26].

Like us, a systematic review showed a lower prevalence of insulin resistance among women, associating it with the protective effect of estrogens[27]. This protective effect of estrogens has also been related to the lower prevalence of NAFLD in women[28,29].

The relationship found in our investigation between the appearance of insulin resistance and belonging to the most disadvantaged socioeconomic levels was also shown in a Colombian study carried out in children[30]. A study of 1081 Japanese students aged 18 to 22 years[31] found that insulin resistance was more prevalent in women belonging to lower socioeconomic levels. A study conducted in Iran gave similar results[32].

A critical review of the literature conducted in India[33] highlighted the effect of tobacco consumption on insulin resistance indicating that exposure to tobacco initiates immune deterioration related to free radicals, DNA damage, and inflammation, which will favor insulin resistance. Some authors[34,35] even speak of a threat to the health of people living in the homes of smokers, since smoke toxins deposited on surfaces can cause insulin resistance.

A study carried out by our group in 219477 workers[36] that also assessed the variables that influenced the appearance of NAFLD showed that advanced age, male sex, and low socioeconomic status increased the risk of presenting NAFLD and liver fibrosis by applying different scales. Smoking, however, demonstrated no influence.

The results of a systematic review and meta-analysis conducted in 2021[37] that included more than one million people concluded that the worldwide prevalence of NAFLD is considerably higher than previously estimated (overall 37.8%: 39.7% in men and 25.6% in women), and continues to increase at an alarming rate; these prevalence data are lower than those found in our study. That study showed that the incidence and prevalence of NAFLD is significantly higher among men than among women, data that coincide with those presented in this study.

The results of a cross-sectional analysis of the National Health and Nutrition Examination Surveys in the United States[38], 2017-2018, which included 3589 participants revealed that the risk of presenting NAFLD was lower among people with higher educational levels and those belonging to more advantaged socioeconomic groups, data similar to those obtained in our study.

The effect of alcohol consumption on the liver has been extensively studied, although this is not the case with smoking. According to one systematic review[39], smoking is both a risk factor for liver fibrosis and a contributing factor to liver carcinogenesis. Smoking-related fibrosis has been observed in patients with NAFLD and other liver pathologies. Excessive smoking causes systemic inflammation, oxidative stress, insulin resistance, and tissue hypoxia, as well as free radical damage. The more than 4000 chemicals in tobacco – including nitrosamines, aromatic hydrocarbons, nicotine, and other alkaloids – have systemic effects on patients in addition to damaging the liver.

As strengths of the study, it is worth highlighting the enormous sample size, more than 418,000 people, which provides great strength to the results obtained; and the large number of risk scales used to assess insulin resistance as well as NAFLD and liver fibrosis.

The main limitation is that no objective techniques were used to assess insulin resistance, NAFLD, and liver fibrosis.

Conclusion

All sociodemographic variables (age, sex, and social class) influence the increased risk of presenting insulin resistance, NAFLD, and liver fibrosis, especially age and sex.

Tobacco use also increases these risks, although to a lesser extent.

The profile of the person at risk for IR, NAFLD, and liver fibrosis would be an older male belonging to social class III and a smoker.

Conflict of Interest

The authors declared that there is no conflict of interest.

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