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Original article

Prevalence and predictors of elevated liver enzyme levels in Mexico: The Mexican National Health and Nutrition Survey, 2016

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ABSTRACT

Introduction and objective: To determine the prevalence of elevated liver enzyme levels and the fatty liver index according to specific sociodemographic, clinical, anthropometric, and metabolic risk factors in Mexican adult population.

Material and methods: The present analysis was conducted using data from the Mexican National Health and Nutrition Survey 2016. For the present study, 3,490 adults with complete information on liver enzymes, sociodemographic, lifestyle, and metabolic factors were analyzed. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) levels were determined from blood samples. We computed the fatty liver Index (FLI), as a surrogate marker of non-alcoholic fatty liver disease. The associations are reported as adjusted odds ratios (OR) and 95% confidence intervals (95%CI).

Results: At the national level, the prevalence of high serum levels of ALT, AST, and GGT were 7.9%, 13.5, and 12.9 respectively. We observed that men had higher prevalences of altered ALT, GGT and FLI compared to women. Additionally, we observe that individuals with obesity, metabolic syndrome and insulin resistance are significantly more likely to present elevated concentrations of AST, ALT, GGT and FLI. Finally, we found that the subjects of the lowest socioeconomic level and indigenous population were more likely to present elevated levels of AST, ALT, GGT, and FLI.

Conclusion: In Mexico, non-alcoholic fatty liver disease affect people with obesity, diabetes, and metabolic syndrome as well as men, subjects of low socioeconomic status, subjects who live in rural areas and indigenous population. Interventions to reduce this condition should be a public health priority.

1. Introduction

During the past decades, remarkable lifestyles changes (i.e. unhealthy diets, sedentarism, physical inactivity, among others) have drastically modified health priorities in most regions of the world, due to a raising incidence in non-communicable diseases (NCDs).[1] Mortality associated with NCDs accounts for 70% of all deaths around the world. Low and middle-income countries are especially affected, where 80% of these deaths occur.[2] Among these, non-alcoholic fatty liver disease (NAFLD), which coincides with the global increase in obesity, is particularly concerning given its silent onset and poor prognosis in advanced stages.[3] NAFLD consists of a range of liver diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH). Simple steatosis is characterized by liver fat infiltration in >5% of the hepatocytes and it is generally asymptomatic, while NASH involves fibrosis and may lead to cirrhosis and hepatocellular carcinoma.[4] The most accepted model for the onset of NAFLD is the "parallel multiple hit theory," which begins with insulin resistance followed by consequent fat accumulation. This leads to secondary

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, gamma-glutamyl transferase; OR, odds ratio; 95% CI, 95% confidence interval; NCD, non-communicable diseases; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2D, type 2 diabetes; ENSANUT MC-2016, Mexican National Health and Nutrition Survey 2016; BMI, body mass index; HbA1C, glycated hemoglobin; FPG, fasting plasma glucose; LDL-c, low-density lipoproteins; HDL-c, high-density lipoproteins; TG, triglycerides; FLI, Fatty Liver Index

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entities including oxidative stress, an inflammatory process, genetic polymorphisms, and altered hepatocyte apoptosis.[5]

The global prevalence of NAFLD is estimated to be 25% and it increases proportionally with the prevalence of obesity.[6] Given the pronounced increase of the combined prevalence of overweight and obesity in Mexico in the past decades (618% to 72.5% from 2000 to 2016), there is special concern regarding the increase of NAFLD.[7] Among other principal known risk factors associated with NAFLD are sex, age, ethnicity, type 2 diabetes (T2D), and certain features of the metabolic syndrome, including insulin resistance, hypertriglyceridemia, abdominal obesity, and low high-density lipoprotein cholesterol, among others.[3,8] Early diagnosis is key to avoid the progression of the disease to more severe stages.

Clinical indicators of liver health are largely based on liver enzyme levels. For instance, liver enzyme concentrations, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) have been used as clinical indicators to screen for liver diseases, including NAFLD.[9] Although not all people with elevated liver enzyme levels have or will progress to NAFLD, this measure is broadly recognized as a proxy for asymptomatic liver disease. Hence, estimating the prevalence of these elevated enzymes at a national level could indicate the magnitude of the disease to inform stakeholders as they design primary prevention programs, policies, interventions, and services for groups who have a higher risk of developing liver disease. In addition, documenting the prevalence of serum biomarkers of liver alteration would help estimate the prevalence of NAFLD, which is key for estimating costs in health care, designing public health interventions, and evaluating the efficacy of future interventions. Moreover, this will help to inform the creation of algorithms specific to the Mexican population, which could be used on a wider scale as part of the national surveys.

Thus, the purpose of this paper was to determine the prevalence of elevated liver enzyme levels (ALT, AST, and GGT) according to specific sociodemographic, clinical, anthropometric, and metabolic risk factors, analyzing data from the Mexican National Health and Nutrition Survey 2016 (ENSANUT MC−2016, by its Spanish acronym).

2. Material and methods

2.1. Design and study population

The present analysis was conducted using data from the ENSANUT MC−2016, a probabilistic population-based survey with multi-stage stratified sampling. The survey is designed to be representative at the national level, by regions, and rural and urban areas. The main aim of the ENSANUT MC−2016 is to quantify the frequency, distribution, and trends of health and nutrition conditions and its determinants. Detailed information on design, sample size, and methodology of the ENSANUT MC−2016 has been described previously.[10] For the present study, 3,490 adults with complete information on liver enzymes, sociodemographic, lifestyle, and metabolic factors were analyzed. Detailed information on the methodology has been previously published.[11]

The present study was developed and performed according to the Declaration of Helsinki guidelines. The Research, Ethics, and Biosecurity Committee at the National Institute of Public Health evaluated and accepted the study protocol and informed consent forms. In addition, we obtained written informed consent from all participants.

2.2. Sociodemographic, lifestyle and metabolic factors

Sociodemographic information, personal and family history of chronic diseases, as well as variables related to lifestyle were obtained through interviews and previously validated questionnaires. Additionally, measurements of height, weight, waist circumference, and blood pressure were collected. The body mass index (BMI) was calculated from the weight (kg) and height (m^2). World Health Organization definitions for normal weight, overweight, and obesity were used. To define abdominal obesity, cut-off points of ≥ 80.0 cm and ≥ 90.0 cm of waist circumference were considered for women and men, respectively. Cut-off points for hypertension were 120 and 90 mmHg for systolic and diastolic blood pressure, respectively.[12]

Smoking status was generated from self-reported information. Smoking status was assessed with the questions 1) “Have you smoked >100 cigarettes in your life?”, and 2) “Are you currently smoking?”. Current smokers were those who answered “yes” to both questions; ever smokers answered “yes” to question 1) and “no” to question 2), and never smoker answered “no” to both questions.

Indigenous population was generated from self-reported information. Indigenous population was constructed with the questions 1) “Do you speak any indigenous language?”, and 2) “According to your culture, do you consider yourself indigenous?”.

The socioeconomic status (SES) was computed using principal components analysis with household characteristics and family assets. In general, SES was constructed by combining eight variables that assessed household characteristics, goods, and available services including: construction materials of the floor, ceiling, and walls; household goods (stove, microwave, washing machine, refrigerator and boiler); and electric goods (television, computer, radio and telephone). The socioeconomic status was divided into tertiles and used as a proxy for low, medium, and high socioeconomic status.

A dichotomous variable for alcohol consumption was generated, with consumers and non-consumers.

Finally, different biomarkers were evaluated in order to define metabolic alterations of interest. Diabetes and pre-diabetes status were defined by glycated hemoglobin (HbA1C) and fasting plasma glucose (FPG) levels according to the American Diabetes Association Guidelines.[13] HbA1C and FPG cut-off points for pre-diabetes were 5.6-6.5% and 100-125 mg/dL, respectively. For T2D, cut-off points were established at levels >6.5% and ≥ 126 mg/dL. The time with diabetes variable included only adults with a previous diagnosis. Hypercholesterolemia, high low-density lipoproteins (LDL-c), low high-density lipoproteins (HDL-c) and hypertriglyceridemia cut-off points were ≥ 200, ≥ 100, < 40 for males and < 50 for females and ≥ 150 mg/dL, respectively.[13]

For the present analysis metabolic syndrome is present if three or more of the following five criteria are met: waist circumference over 90 cm (men) or 80 cm (women), blood pressure over 130/85 mmHg, fasting triglycerides (TG) level over 150 mg/dL, fasting HDL-c level less than 40 mg/dL (men) or 50 mg/dL (women) and FPG over 100 mg/dL.

2.3. Liver enzyme analysis

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) levels were determined from blood samples obtained from participants after fasting for 8 hours. Blood samples were obtained and collected in a tube to obtain serum after they were centrifuged in-situ. Serum was stored in cryotubes and transported in nitrogen to the INSP laboratory, where they were stored at -70°C until analysis. Analyses were performed at the National Nutrition and Medical Sciences Institute. AST and GGT were analyzed by enzymatic methods. ALT was measured by the kinetic method with UniCel DxC 600 Syncron® Clinical system.

Elevated serum transaminases were defined as ALT ≥ 30 U/L in men and ≥ 19 U/L in women, AST ≥ 37 U/L in men and ≥ 31 U/L in women, or GGT > 48 U/L both in men and women.[14−16]

2.4. Fatty Liver Index

For the present study, we computed the fatty liver Index (FLI), a surrogate marker of NAFLD.[17,18] FLI was computed using the following formula:

$$FLI = (e^{0.953*loge(triglycerides) + 0.139*BMI + 0.718*loge(GGT) + 0.053*waistcircumference - 15.745})/(1 + e^{0.953*loge(triglycerides) + 0.139*BMI + 0.718*loge(GGT) + 0.053*waistcircumference - 15.745}) * 100.$$

In this case, as reported by Bedogni, et al., a FLI ≥ 60 ruled in NAFLD.

2.5. Statistical analysis

Descriptive analyses of the main characteristics of interest stratified by normal and elevated liver enzyme levels were performed. Age-adjusted prevalence of elevated serum transaminases were estimated by sociodemographic characteristics, lifestyle and metabolic factors, as well as chronic diseases.

The associations are reported as adjusted odds ratios (adjusted for: age, sex, smoking status, alcohol consumption, education level, area, SES, region, BMI, T2D, hypertension, and metabolic syndrome). To account for unequal selection probabilities from the study design and complexity of survey data, all statistical analyses were performed with module SVY of Stata statistical software version 14.0. A value of $P < 0.05$ was considered to be statistically significant.

3. Results

Table 1 presents the prevalence of elevated liver enzyme serum levels according to sociodemographic characteristics of interest nationally and comparing by sex. At the national level, people with elevated AST serum levels were more likely to be younger (13.8 [95% CI: 9.8, 17.8], 14.4 [95% CI: 10.3, 18.4], 14.8 [95% CI: 10.5, 19.1], 12.8 [95% CI: 8.2, 17.4]; in subjects 30-39, 40-49, 50-59, and 60-69 years

Table 1
Prevalence of elevated transaminases by sociodemographic characteristics in adult Mexican population, ENSANUT MC-2016.

Characteristic	Elevated ALT[δ] %	95% CI	Elevated AST[Ω] %	95% CI	Elevated GGT[Σ] %	95% CI	NAFLD[∂] %	95% CI
Age group								
20-29	10.8	[6.4, 15.1]	12.0	[7.8, 16.2]	9.6	[5.1, 14.0]	43.7	[37.0, 50.7]
30-39	10.4	[6.6, 14.1]	13.8	[9.8, 17.8]	9.9	[6.7, 13.1]	50.8	[43.3, 58.3]
40-49	6.9	[4.6, 9.1]	14.4	[10.3, 18.4]	15.3	[10.6, 19.9]	52.3	[45.8, 58.6]
50-59	6.3	[3.8, 8.8]	14.8	[10.5, 19.1]	20.7	[14.1, 27.3]	66.2	[59.7, 72.1]
60-69	2.9	[1.4, 4.3]	12.8	[8.2, 17.4]	11.9	[7.4, 16.3]	58.9	[53.5, 64.2]
Sex								
Female	7.4	[5.4, 9.3]	14.6	[12.1, 17.0]	9.8	[7.5, 12.0]	51.8	[47.9, 55.7]
Male	8.4	[6.0, 10.8]	12.3	[9.4, 15.2]	16.0	[12.6, 19.4]	54.7	[49.6, 59.6]
Education[Ψ]								
<Elementary	9.2	[2.9, 15.5]	16.6	[10.5, 22.7]	12.2	[5.1, 19.2]	54.9	[47.4, 62.2]
Elementary	7.5	[5.5, 9.4]	16.8	[13.1, 20.6]	12.0	[8.9, 15.0]	57.9	[53.5, 62.3]
Secondary	8.8	[6.0, 11.6]	14.7	[11.0, 18.4]	15.2	[10.7, 19.7]	56.2	[50.2, 62.1]
High school	7.0	[3.4, 10.5]	10.2	[6.0, 14.4]	14.0	[8.8, 19.2]	46.8	[40.1, 53.7]
≥High school	7.5	[2.5, 12.5]	7.4	[3.3, 11.5]	9.1	[3.9, 14.3]	45.5	[33.5, 58.2]
Socioeconomic status[∋Ψ]								
Low	11.5	[8.2, 14.8]	22.6	[18.4, 26.8]	16.4	[12.4, 20.5]	53.5	[48.0, 59.1]
Medium	9.2	[6.2, 12.2]	14.2	[10.6, 17.7]	13.0	[9.8, 16.2]	54.4	[49.7, 59.1]
High	5.2	[3.2, 7.1]	8.7	[6.2, 11.2]	11.2	[7.8, 14.5]	50.8	[46.3, 55.3]
Place of residence[Ψ]								
Rural	9.0	[7.2, 11.2]	16.7	[14.0, 19.7]	13.1	[10.9, 15.7]	49.9	[46.6, 53.4]
Urban	7.5	[5.9, 9.6]	12.5	[10.4, 15.0]	12.8	[10.3, 15.8]	54.2	[50.3, 58.0]
Region[Ψ]								
North	7.1	[4.7, 10.8]	10.5	[8.2, 13.5]	9.1	[5.5, 14.9]	51.1	[45.8, 56.4]
Central	8.3	[5.5, 12.3]	13.4	[10.2, 17.4]	12.5	[9.0, 17.1]	51.4	[44.8, 58.0]
Mexico City	2.2	[1.0, 5.5]	9.5	[4.9, 17.7]	13.6	[8.3, 21.6]	56.7	[47.4, 65.4]
South	11.9	[9.6, 14.7]	19.0	[15.7, 22.7]	16.4	[13.4, 19.9]	55.0	[50.7, 59.3]
Indigenous population								
No	5.6	[4.2, 7.3]	10.5	[8.7, 12.6]	12.2	[9.7, 15.0]	50.1	[48.7, 52.9]
Yes	13.1	[10.1, 16.7]	20.1	[16.2, 24.7]	14.6	[10.9, 19.2]	54.2	[49.2, 59.2]
Smoker[Ψ]								
No	6.8	[3.4, 10.2]	12.2	[7.6, 16.7]	12.5	[7.7, 17.3]	51.2	[47.2, 55.4]
Yes	9.1	[6.2, 12.0]	13.7	[10.0, 17.4]	11.8	[9.2, 14.5]	57.7	[51.6, 63.5]
Alcohol consumption[Ψ]								
No	7.5	[5.7, 9.2]	13.0	[10.7, 15.3]	10.2	[7.9, 12.5]	51.2	[44.6, 57.7]
Yes	8.8	[5.8, 11.8]	14.6	[11.0, 18.2]	20.1	[15.2, 25.1]	54.0	[50.5, 57.5]

[Ψ] Prevalence adjusted by age as continuous.
[δ] Elevated Alanine aminotransferase; ≥ 30 U/L in men and ≥ 19 U/L in women.
[Ω] Elevated Aspartate aminotransferase; ≥ 37 U/L in men and ≥ 31 U/L in women.
[Σ] Elevated Gamma-glutamyl transferase; ≥ 48 U/L both in men and women.
[∂] Elevated Fatty Liver Index; ≥ 60 ruled in non-alcoholic fatty liver disease (NAFLD).
[∋] The socioeconomic status variable (SES) was created using principal components analysis with household characteristics and family assets. The SES was divided into tertiles and used as a proxy for low, medium, and high SES.

Table 2
Prevalence of elevated transaminases by anthropometric and metabolic characteristics in adult Mexican population, ENSANUT MC-2016.

Characteristic	Elevated ALT[δ]		Elevated AST[Ω]		Elevated GGT[Σ]		NAFLD[∂]	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
BMI category[Ψ]								
<25 Kg/m^2	4.4	[2.3, 6.4]	8.1	[5.6, 10.6]	8.9	[5.5, 12.2]	7.8	[4.9, 12.4]
≥25 Kg/ m^2 and < 30 Kg/m^2	7.1	[4.7, 9.5]	12.7	[9.6, 15.8]	13.3	[10.0, 16.6]	45.5	[40.0, 51.1]
≥30 Kg/m^2	11.6	[8.3, 15.0]	18.6	[14.6, 22.5]	16.0	[11.5, 20.5]	90.1	[87.2 93.6]
Abdominal obesity[Ψ]								
< 80cm for women or < 90cm for men	3.6	[1.7, 5.6]	8.7	[5.5, 12.0]	10.6	[6.2, 14.9]	5.4	[2.8, 10.2]
≥ 80cm for women or ≥ 90cm for men	9.3	[7.2, 11.4]	15.1	[12.7, 17.6]	13.9	[11.1, 16.8]	64.9	[61.5, 68.2]
Hypertension[Ψ]								
No (< 140/90 mmHg)	7.7	[6.0, 9.4]	13.2	[11.0, 15.3]	12.2	[9.7, 14.8]	44.3	[40.6, 48.0]
Yes (>140/90 mm Hg)	10.1	[6.2, 14.1]	16.1	[11.6, 20.6]	16.3	[10.1, 22.5]	69.0	[64.2, 73.4]
Diabetes status[Ψ]								
Normal (<100 mg/dL or HbA1C < 5.6)	6.8	[4.9, 8.7]	11.7	[9.2, 14.1]	8.2	[6.0, 10.5]	43.2	[39.2, 47.3]
Prediabetes (100-125 mg/dL or HbA1C 5.6-6.5)	8.2	[5.7, 10.7]	14.3	[11.1, 17.6]	16.8	[11.4, 22.2]	64.0	[58.2, 69.4]
Diabetes (>=126 or HbA1C >6.5 or previous diagnosis)	13.5	[8.0, 19.0]	18.8	[12.9, 24.8]	24.1	[17.3, 30.9]	73.0	[66.9, 78.3]
Time with diagnosis of diabetes[Ψ]								
Survey finding	14.2	[6.9, 21.5]	24.5	[10.9, 38.1]	31.1	[16.9, 45.4]	83.4	[73.4, 90.4]
< 5 years	12.5	[3.4, 21.5]	22.7	[11.9, 33.5]	28.0	[15.2, 40.8]	75.4	[63.5, 84.4]
5-10 years	9.9	[3.2, 16.7]	15.9	[8.4, 23.3]	16.2	[7.3, 25.0]	73.5	[62.9, 82.0]
> 10 years	2.5	[-0.2, 5.2]	12.6	[3.0, 22.3]	13.2	[6.6, 19.9]	56.5	[41.7 70.3]
Hypercholesterolemia[Ψ]								
No (Total Cholesterol < 200 mg/dL)	6.9	[5.2, 8.5]	12.9	[10.3, 15.4]	11.4	[8.7, 14.0]	48.6	[44.5, 52.7]
Yes (Cholesterol >200 mg(dL)	10.0	[7.3, 12.8]	14.6	[11.6, 17.5]	15.6	[12, 19.2]	61.4	[56.6, 66.0]
High LDL (mg/dL) [Ψ]								
< 100 mg/dL	6.5	[4.1, 8.9]	13.3	[10.0, 16.5]	13.3	[9.0, 17.6]	48.5	[43.3, 53.8]
≥ 100 mg/dL	8.3	[6.3, 10.3]	12.3	[10.2, 14.5]	11.3	[9.2, 13.5]	51.4	[47.7, 55.1]
Low HDL (mg/dL) [Ψ]								
≥40 mg/dL for men and ≥ 50 for women	6.6	[4.4, 8.9]	10.7	[8.4, 13.0]	11.3	[8.4, 14.2]	36.2	[30.8, 41.9]
< 40 mg/dL for men and < 50 for women	8.8	[6.7, 10.8]	15.4	[12.5, 18.3]	14.0	[11.1, 16.8]	58.5	[54.8, 62.1]
Hypertriglyceridemia (mg/dL) [Ψ]								
< 150 mg/dL	4.4	[2.8, 6.0]	8.8	[6.5, 11.0]	8.7	[6.2, 11.2]	27.6	[23.9, 31.6]
≥ 150 mg/dL	10.7	[8.2, 13.3]	17.0	[14.2, 19.9]	16.0	[12.8, 19.1]	72.3	[68.3, 75.9]
Metabolic syndrome[∝Ψ]								
No	3.5	[2.1, 4.9]	7.7	[5.6, 9.7]	7.4	[5.2, 9.6]	14.5	[11.6, 18.0]
Yes	11.7	[8.8, 14.7]	18.0	[14.7, 21.2]	17.5	[13.8, 21.2]	75.1	[71.8, 78.2]
Insulin resistance (HOMAIR ≥90 percentile)[Ψ]								
No	7.1	[5.6, 8.6]	12.1	[10.3, 13.9]	11.0	[9.0, 13.0]	48.9	[45.9, 52.1]
Yes	14.4	[9.0, 19.8]	24.5	[17.3 31.7]	28.0	[16.6, 39.4]	88.1	[81.2, 92.7]

[δ] Elevated Alanine aminotransferase; ≥ 30 U/L in men and ≥ 19 U/L in women.
[Ω] Elevated Aspartate aminotransferase; ≥ 37 U/L in men and ≥ 31 U/L in women.
[Σ] Elevated Gamma-glutamyl transferase; ≥ 48 U/L both in men and women.
[∂] Elevated Fatty Liver Index; ≥ 60 ruled in non-alcoholic fatty liver disease (NAFLD).
[∝] For the present analysis metabolic syndrome is present if three or more of the following five criteria are met: waist circumference over 90 cm (men) or 80 cm (women), blood pressure over 130/85 mmHg, fasting TG level over 150 mg/dL, fasting HDL-c level less than 40 mg/dL (men) or 50 mg/dL (women) and fasting blood glucose over 100 mg/dL.

respectively). According to the region, the age-sex adjusted prevalence in those subjects with high serum levels of ALT were higher in the Southern region (11.8%; 95% CI: 9.4, 14.2), while the lowest prevalence was observed in Mexico City (2.3%; 95% CI: 0.3, 4.2). According to socioeconomic status, those with a low SES had a higher prevalence of AST (2.6%; 95% CI: 18.4, 26.8) compared to those with high SES (8.7%; 95% CI: 6.2, 11.2). Finally, with respect to place of residence, individuals living in rural areas were more likely to have elevated GGT compared to individuals living in urban areas.

Comparing by sex, males from the South of the country had a higher prevalence of elevated ALT (13.1%; 95% CI: 8.8, 17.4) than their male counterparts from the Central region (9.2; 95% CI: 13.8, 14.6), Northern region (6.4; 95% CI: 2.8, 10.1), and Mexico City (2.1%; 95% CI: 1.5, 5.8). We also observed that females living in rural areas were more likely to have elevated ALT, AST, GGT levels compared to females living in urban areas (See Table 1, Supplementary Table 1).

At the national level, after adjustment for age and sex, 11.6% (95% CI: 8.3, 15.0) of subjects with a BMI ≥ 30.0 kg/m^2 had higher serum levels of ALT, while only 4.4% (95% CI: 2.3, 6.4) of subjects with a normal BMI (< 25.0 kg/m^2) had elevated concentrations of ALT. The prevalence of high serum levels of AST was greater among subjects with abdominal obesity (15.1%; 95% CI: 12.7, 17.1), with low HDL–c concentration (15.4%; 95% CI: 12.5, 18.3), and hypertriglyceridemia (17.0%; 95% CI: 14.2, 19.9) (Table 2).

We found that males with obesity had a higher prevalence than their female counterparts (13.6 [95% CI: 7.8, 19.3] vs. 10.2% [95% CI: 6.2, 14.2]). Similar results were observed for elevated GGT levels (23.8 [95% CI: 15.6, 32.0] vs. 10.5% [95% CI: 6.8, 14.2]). When evaluating the prevalence of elevated ALT serum levels by sex and diabetes status, we observed that females with diabetes had a higher prevalence than their male counterparts (14.6 [95% CI: 7.6, 21.7] vs. 11.9% [95% CI: 4.6, 19.1]) (See Table 2, Supplementary Table 2).

Adjusted odds ratios according to sociodemographic risk factors and elevated concentrations of ALT, AST, and GGT are presented in Table 3. With respect to ALT, we found that subjects with low SES were significantly more likely to present elevated concentrations of ALT than individuals with high SES (OR = 2.58; 95% CI: 1.34, 5.05). Regarding AST, we observed that individuals with low SES were significantly more likely to have elevated concentrations of AST (OR = 3.34; 95% CI: 2.08, 5.40) than individuals with high SES. With respect to ALT, we found that indigenous population were significantly more likely to present elevated concentrations of ALT than non-indigenous population (OR = 2.58; 95% CI: 1.42, 4.69). Regarding AST, we observed that indigenous population were significantly more likely to have elevated concentrations of AST (OR = 2.65; 95%

Table 3
Association between sociodemographic characteristics and elevated alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase in adult Mexican population, ENSANUT MC-2016.

Characteristic	Elevated ALT				Elevated AST				Elevated GGT			
	Crude		Adjusted[Φ]		Crude		Adjusted		Crude		Adjusted	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Sex												
Male	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Female	0.87	(0.56, 1.36)	0.93	(0.50, 1.76)	1.21	(0.86, 1.70)	1.46	(0.93, 2.29)	0.56	(0.41, 0.78)	0.51	(0.32, 0.82)
Age												
< 39 years	2.39	(1.35, 4.22)	2.83	(1.52, 5.23)	1.16	(0.74, 1.84)	1.25	(0.79, 2.10)	1.61	(0.93, 2.76)	1.92	(1.04, 3.51)
40-59 years	3.99	(2.22, 7.16)	5.56	(2.74, 10.93)	1.01	(0.61, 1.67)	1.15	(0.61, 1.99)	0.80	(0.51,1.26)	1.15	(0.60, 2.16)
≥60 years	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Region												
North	3.51	(1.31, 9.37)	3.68	(1.35, 10.15)	1.12	(0.53, 2.37)	1.09	(0.56, 2.19)	0.64	(0.29, 1.38)	0.55	(0.21, 1.31)
Center	4.08	(1.53, 10.85)	4.21	(1.56, 11.47)	1.47	(0.67, 3.15)	1.55	(0.74, 3.15)	0.91	(0.47, 1.74)	0.84	(0.40, 1.82)
Mexico City	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
South	6.13	(2.47, 15.19)	5.69	(2.20, 14.91)	2.23	(1.07, 4.64)	1.82	(0.94, 3.65)	1.24	(0.68, 2.24)	1.10	(0.53, 2.29)
Urbanicity												
Rural	1.37	(0.92, 2.04)	0.80	(0.56, 1.27)	1.52	(1.10, 2.10)	0.90	(0.63, 1.29)	1.08	(0.75, 1.54)	0.78	(0.52, 1.24)
Urban	1.65	(0.92, 2.95)	1.28	(0.70, 2.39)	1.43	(0.93, 2.21)	1.18	(0.71, 1.90)	1.25	(0.75, 2.07)	1.19	(0.69, 2.12)
Metropolitan	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Socioeconomic status[∋]												
Low	2.56	(1.53, 4.28)	2.58	(1.34, 5.05)	3.00	(2.00, 4.51)	3.34	(2.08, 5.40)	1.52	(0.97, 2.38)	1.80	(1.01, 3.18)
Medium	1.89	(1.13, 3.18)	1.89	(1.09, 3.27)	1.72	(1.11, 2.66)	1.85	(1.19, 2.94)	1.18	(0.75, 1.84)	1.19	(0.72, 1.91)
High	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Indigenous population												
No	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–
Yes	2.55	[1.67, 3.88]	2.58	[1.42, 4.69]	2.15	[1.54, 2.99]	2.65	[1.64, 4.27]	1.44	[1.01, 2.07]	1.61	[1.07, 2.54]
Smoker												
No	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes	1.20	(0.63, 2.28)	1.40	(0.75, 2.61)	1.14	(0.67, 1.95)	1.15	(0.71, 1.92)	1.01	(0.62, 1.61)	1.13	(0.61, 1.90)
Alcohol use												
No	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes	1.38	(0.87, 2.19)	1.26	(0.80, 2.17)	1.11	(0.7, 1.58)	1.39	(0.94, 2.16)	1.99	(1.35, 2.95)	1.80	(1.11, 2.84)

[δ] Elevated Alanine aminotransferase; ≥ 30 U/L in men and ≥ 19 U/L in women.
[Ω] Elevated Aspartate aminotransferase; ≥ 37 U/L in men and ≥ 31 U/L in women.
[Σ] Elevated Gamma-glutamyl transferase; ≥ 48 U/L both in men and women.
[∋] The socioeconomic status variable (SES) was created using principal components analysis with household characteristics and family assets. The SES was divided into tertiles and used as a proxy for low, medium, and high SES.
[Φ] Adjusted by: age, sex, region, place of residence, socioeconomic status, alcohol intake, smoking status, indigenous population.

CI: 1.64, 4.27) than non-indigenous population. Finally, we observed that indigenous population were significantly more likely to have elevated concentrations of GGT (OR = 1.61; 95% CI: 1.07, 2.54) than non-indigenous population.

We observed that individuals with hypertriglyceridemia are significantly more likely to present elevated concentrations of AST (OR = 2.64; 95% CI: 1.59, 4.40) compared to those without hypertriglyceridemia. In the GGT analysis, we observed that pre-diabetic (OR = 2.24; 95% CI: 1.23, 4.08) and diabetic (OR = 5.93; 95% CI: 3.22, 10.92) individuals are more likely to have elevated GGT serum levels compared to subjects with normal glucose serum levels (Table 4).

Finally, we found that individuals with insulin resistance had approximately 8 times higher odds of NAFLD (Table 5).

4. Discussion

Based on the results, there is clear evidence that the prevalence of high ALT, AST, and GGT levels and high scores (≥ 60) of FLI among the Mexican population could be driven by metabolic diseases, such as diabetes, insulin resistance, and obesity.

The present analysis examined the association between elevated ALT, AST, and GGT, and specific sociodemographic, clinical, anthropometric and metabolic risk factors in a cross-sectional, nationally representative study. The findings derived from 3,490 ALT, AST, and GGT measurements in an adult population indicate a high prevalence of elevated aminotransferases: 7.9% for ALT; 13.5 for AST; and 12.9 for GGT, for the overall population. These results were similar to a previous studies conducted in Mexican population.[19–21]

Regarding the FLI, we found that, in our sample, the prevalence of NAFLD was 53.2% (51.8% and 54.7 for women and men respectively) which was in agreement to a previous studies in Mexico (46% and 49%).[19,20]

According to sex, in general, males showed a higher prevalence of elevated aminotransferases than their female counterparts. For example, 8.4% of males and 7.4% of females had elevated concentrations of ALT, while 16.1% of males and 9.8% of females had high levels of GGT. With respect to sociodemographic risk factors, the strongest determinant of elevated ALT, AST, and GGT was low socioeconomic status. Female sex was negatively associated with higher concentrations of ALT and GGT. Moreover, age was also negatively related. Among the metabolic, anthropometric and clinical risk factors, the most important determinants of elevated ALT, AST and GGT were an increased waist circumference and BMI. Other independent predictors were pro-atherogenic lipids such as high levels of triglycerides and low concentrations of HDL–c. Finally, those individuals with diabetes, metabolic syndrome or insulin resistance were more likely to have elevated aminotransferases levels. In general, our findings are similar to other studies that have investigated the predictors and prevalence of elevated aminotransferase activity as a proxy for NAFLD among adults.[14,22–24]

In agreement with previous studies,[25,26] our results indicate that individuals under the age of 60 have a significantly higher risk of elevated ALT. Our data suggest that individuals between 40-59 years had more than 5 times greater odds of elevated ALT concentrations, while subjects <30 years had approximately 3 times greater odds, compared with individuals ≥60 years. This result may be explained by a loss of skeletal muscle mass in elderly populations as some ALT

Table 4
Association between metabolic and anthropometric abnormalities and elevated alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase in adult Mexican population, ENSANUT MC-2016.

Characteristic	Elevated ALT Crude		Adjusted[Φ]		Elevated AST Crude		Adjusted		Elevated GGT Crude		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
BMI category												
<25.0 Kg/m^2	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
≥25.0 Kg/ m^2 and < 30.0 Kg/m^2	1.52	(0.81, 2.86)	1.93	(0.80, 4.64)	1.66	(1.04, 2.64)	2.02	(1.01, 4.07)	1.60	(0.96, 2.66)	1.47	(0.74, 2.90)
≥30.0 Kg/m^2	2.63	(1.47, 4.69)	2.69	(1.22, 5.93)	2.59	(1.71, 3.92)	3.07	(1.63, 5.75)	1.99	(1.20, 3.30)	1.99	(1.011, 4.05)
Abdominal obesity												
No, (< 80 cm for women or < 90 cm for men)	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes, (≥ 80 cm for women or ≥ 90 cm for men)	2.19	(1.21, 3.99)	3.18	(1.36, 7.42)	1.86	(1.19, 2.90)	2.24	(1.11, 4.56)	1.45	(0.84, 2.49)	1.50	(0.80, 3.71)
Hypertension												
No (< 140/90 mmHg)	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes (≥140/90 mm Hg)	1.05	(0.69, 1.58)	1.90	(1.06, 3.38)	1.27	(0.91, 1.76)	1.69	(1.01, 2.83)	1.52	(1.00, 2.32)	1.25	(0.74, 2.10)
Diabetes status												
Normal (glucose <100 mg/dL or HbA1c < 5.6)	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Prediabetes (glucose 100-125 mg/dL or HbA1c 5.6-6.5)	0.91	(0.58, 1.40)	0.88	(0.46, 1.48)	1.23	(0.87, 1.74)	1.01	(0.59, 1.70)	2.20	(1.39, 3.45)	2.24	(1.23, 4.08)
Diabetes (glucose ≥126 mg/dL or HbA1c ≥6.5 or previous diagnosis)	1.24	(0.76, 2.03)	1.89	(1.03, 3.63)	1.68	(1.08, 2.61)	1.92	(1.11, 3.33)	3.40	(2.19, 5.23)	5.93	(3.22, 10.92)
Hipercholesterolemia												
No (Total Cholesterol < 200 mg/dL)	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes (Cholesterol ≥200 mg/dL)	1.26	(0.86, 1.85)	1.82	(1.04, 3.23)	1.17	(0.84, 1.62)	1.24	(0.72, 2.11)	1.51	(1.05, 2.16)	1.57	(1.01, 2.43)
Elevated LDL-c												
No, (< 100 mg/dL)	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes, (≥ 100 mg/dL)	1.14	(0.71, 1.81)	1.13	(0.56, 2.19)	0.94	(0.66, 1.33)	0.84	(0.44, 1.26)	0.90	(0.58, 1.37)	0.66	(0.36, 1.15)
Low HDL-c												
No, (≥50 mg/dL for women or ≥40 mg/dL for men)	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes, (<50 for women or < 40 mg/dL for men)	1.51	(0.88, 2.59)	1.62	(0.88, 3.36)	1.45	(0.98, 2.12)	1.43	(0.88, 2.56)	0.98	(0.64, 1.51)	1.15	(0.52, 1.65)
Hypertriglyceridemia												
No, (< 150 mg/dL)	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes, (≥ 150 mg/dL)	2.36	(1.44, 3.84)	3.04	(1.49, 6.18)	2.14	(1.53, 2.97)	2.64	(1.59, 4.40)	2.04	(1.41, 2.96)	1.86	(1.11, 3.09)
Metabolic Syndrome[∝]												
No	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes	2.62	(1.60, 4.30)	3.34	(1.67, 6.70)	2.54	(1.78, 3.65)	3.36	(1.80, 6.24)	2.65	(1.76, 3.98)	2.13	(1.27, 3.59)
Insuline resistance (HOMAIR ≥90 percentile)												
No	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes	2.10	(1.31, 3.35)	2.12	(1.15, 3.83)	2.42	(1.56, 3.75)	3.20	(1.80, 5.69)	3.17	(1.73, 5.81)	3.62	(1.86, 7.03)

[δ] Elevated Alanine aminotransferase; ≥ 30 U/L in men and ≥ 19 U/L in women.
[Ω] Elevated Aspartate aminotransferase; ≥ 37 U/L in men and ≥ 31 U/L in women.
[Σ] Elevated Gamma-glutamyl transferase; ≥ 48 U/L both in men and women.
[∝] For the present analysis metabolic syndrome is present if three or more of the following five criteria are met: waist circumference over 90 cm (men) or 80 cm (women), blood pressure over 130/85 mmHg, fasting TG level over 150 mg/dL, fasting HDL-c level less than 40 mg/dL (men) or 50 mg/dL (women) and fasting blood glucose over 100 mg/dL.
[Φ] Adjusted by: age, sex, region, place of residence, socioeconomic status, alcohol intake, smoking status, indigenous population.

is muscle-derived; others propose that ALT may be a novel biomarker of aging.[27]

Contrary to previous studies[28,29] which describes that individuals with high socioeconomic status had lower odds of elevated liver enzyme levels, as well as NAFLD, our findings showed that individuals with low socioeconomic status had nearly threefold higher odds of having elevated concentrations of ALT than individuals with high socioeconomic status (95% CI: 1.34, 5.05). According to AST, we observed that individuals with low socioeconomic status had three times higher odds of having elevated AST concentrations (OR = 3.34; 95% CI: 2.08, 5.40) than individuals with high socioeconomic status.

We found a higher prevalence of elevated liver enzymes among overweight and obese subjects. Our data suggest a prevalence of elevated ALT of 7.1% and 11.6% among overweight and obese individuals, while the prevalence of elevated AST was 12.7% in people with overweight and 18.6% with obesity. The relationship between elevated liver enzymes and obesity has been well described previously. [24,25,30,31] In this case, we observed an approximately 2.7-fold, 3.0-fold, and 2.0-fold increased odds of elevated ALT, AST and GGT respectively among individuals with obesity. For ALT, our result is similar to those found by Flores et al., who reported an OR of 6.07 for Mexican-American adults with obesity participating in the National Health and Nutrition Survey.

We and others have reported the high prevalence of elevated liver enzymes and NAFLD among individuals with metabolic syndrome [32,33] and its components, including insulin resistance. In the current analysis, multiple individual components of metabolic syndrome, like abdominal obesity, high fasting glucose, hypertriglyceridemia, and low levels of HDL-c are independent predictors of elevated liver enzyme levels. Comparing liver enzyme concentrations between subjects with and without metabolic syndrome, our results confirmed that ALT, AST, and GGT levels among individuals with metabolic syndrome were far higher than those without metabolic syndrome. For example, in subjects with metabolic syndrome, we observed an OR of 3.34, 3.36, and 2.13 of elevated ALT, AST and GGT, respectively. Our results are comparable to those of a population-based study of Latinos in the U.S., which reported a higher prevalence of elevated ALT among those with metabolic syndrome.[30]

We found a higher prevalence of elevated liver enzymes among subjects with pre-diabetes and diabetes. Our data suggest a prevalence of elevated ALT of 8.2% and 13.5% among individuals with prediabetes and diabetes, while the prevalence of elevated AST was 14.3% in subjects with pre-diabetes and 18.8% in individuals with diabetes. Also, a prevalence of elevated GGT of 16.8% and 24.1% among subjects living with pre-diabetes and diabetes was found. Additionally, we observed an approximately 1.9−fold, 1.9−fold, and 5.9-fold

Table 5
Association between metabolic abnormalities and elevated fatty liver index (≥ 60) in adult Mexican population, ENSANUT MC-2016.

Characteristic	Nonalcoholic fatty liver disease[∂]			
	Crude		Adjusted[Φ]	
	OR	(95% CI)	OR	(95% CI)
Hypertension				
No (< 140/90 mmHg)	1.0	Reference	1.0	Reference
Yes (≥140/90 mm Hg)	2.80	(2.18, 3.62)	2.70	(1.71, 4.27)
Diabetes status				
Normal (glucose <100 mg/dL or HbA1c < 5.6)	1.0	Reference	1.0	Reference
Prediabetes (glucose 100-125 mg/dL or HbA1c 5.6-6.5)	2.34	(1.76, 3.11)	2.20	(1.48, 3.27)
Diabetes (glucose ≥126 mg/dL or HbA1c ≥6.5 or previous diagnosis)	3.55	(2.49, 5.07)	3.62	(2.08, 6.32)
Hipercholesterolemia				
No (Total Cholesterol < 200 mg/dL)	1.0	Reference	1.0	Reference
Yes (Cholesterol ≥200 mg(dL)	1.68	(1.29, 2.20)	1.72	(1.17, 2.53)
Elevated LDL-c				
No, (< 100 mg/dL)	1.0	Reference	1.0	Reference
Yes, (≥ 100 mg/dL)	1.12	(0.88, 1.44)	1.14	(0.81, 1.58)
Low HDL-c				
No, (≥50 mg/dL for women or ≥40 mg/dL for men)	1.0	Reference	1.0	Reference
Yes, (<50 for women or < 40 mg/dL for men)	2.66	(2.09, 3.40)	2.53	(1.74, 3.70)
Insuline resistance (HOMAIR ≥90 percentile)				
No	1.0	Reference	1.0	Reference
Yes	7.74	(4.51, 13.29)	7.86	(3.53, 12.17)

[∂] Elevated Fatty Liver Index; ≥ 60 ruled in non-alcoholic fatty liver disease.
[Φ] Adjusted by: age, sex, region, place of residence, socioeconomic status, alcohol intake, smoking status, indigenous population.

increased odds of elevated ALT, AST and GGT respectively among individuals living with diabetes. For ALT, our results are similar to findings from Flores et al., who reported an OR of 2.1 in adults with diabetes participating in a cohort of Mexican health workers.[21]

Our study has some limitations. First, it was a cross-sectional study; thus, we cannot determine causality or temporality between the risk factors studied and elevated liver enzyme levels. Second, we present the associations observed in prevalent cases, which may be different from the associations in incident cases. Third, due to the fact that people with more severe forms of disease may have been less likely to participate in ENSANUT MC-2016, we cannot rule out the possibility of selection bias. However, this bias would result in an underestimation of the association observed between risk factors and elevated levels of ALT, AST, and GGT. On the other hand, strengths of this study included the large sample size, the population-based study design, the homogeneous ethnic background, and the high participation rate.

To the extent that elevated ALT, AST, and GGT activity may reflect underlying liver disease such as NAFLD,[34] our findings indicate that a significant number of Mexican adults are at a high risk of developing liver disease. Considering that the rates of obesity, diabetes, and other metabolic alterations have been rising gradually over the last 2 decades, and on the basis of our results, we might expect a parallel increase in the number of people with elevated liver enzyme levels and consequently, in the prevalence of NAFLD and other liver diseases.

In Mexico, the prevalence of elevated liver enzyme levels is high (7.9% for ALT, 13.5 for AST, and 12.9 for GGT, for the overall population). Furthermore, NAFLD significantly affect younger adults and individuals with low socioeconomic status. In terms of metabolic and anthropometric characteristics, NAFLD affect people with high BMI, diabetes, metabolic syndrome, and insulin resistance. In this sense, due to the high rates of obesity, diabetes, and metabolic syndrome in our population, interventions to reduce this condition and some of its health consequences should be a public health priority. Finally, more studies to develop effective treatment options and programs for people with elevated liver enzymes are necessary. In addition, given the high prevalence of elevated liver enzymes, the use of assessment tools, like the FLI, can detect early stages of NAFLD and other liver diseases among the general population would be beneficial for future research.

Availability of data and material

The datasets generated during and/or analyzed during the current study are not publicly available due to protecting participant confidentiality, but are available from the corresponding author or Dr. Edgar Denova-Gutiérrez. Data are from the Mexican National Health and Nutrition Survey 2016 whose authors may be contacted at: edenovag@gmail.com or edgar.denova@insp.mx

Authors' contributions

The authors' contributions were as follows: S.B, C.A-S., M.H-A., and E.D-G., designed research; S.B, C.A-S., D.K. and E.D-G., conducted research; E.D-G., L.L-C., C.H-A., analyzed data or performed statistical analysis; E.D-G, wrote paper; all authors reviewed the manuscript, and all authors had primary responsibility for final content

Conflicts of interest

The authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.aohep.2021.100562.

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