# High prevalence of non-alcoholic fatty liver disease and metabolic risk factors in Guatemala: A population-based study

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**Abstract**   *Background:* There are no data on the prevalence of non-alcoholic fatty liver disease (NAFLD) in general population samples in Guatemala or in other Central American countries. The prevalence and distribution of NAFLD and its associated risk factors were evaluated in a population-based sample of adults in Guatemala.
*Methods:* Cross-sectional study of 411 men and women 40 years of age or older residing in urban and rural areas of Guatemala. Metabolic outcomes included obesity, central obesity, hypercholesterolemia, diabetes, and metabolic syndrome (MetS). Liver disease outcomes included elevated liver enzymes, elevated Fatty Liver Index (FLI), and elevated FIB-4 score.
*Results:* The overall prevalence of obesity, central obesity, diabetes, and MetS were 30.9, 74.3, 21.6, and 64.2%, respectively. The fully-adjusted prevalence ratios (95% CI) for obesity, central obesity, diabetes, and MetS comparing women to men were 2.83 (1.86—4.30), 1.72 (1.46—2.02), 1.18 (1.03—1.34), and 1.87 (1.53—2.29), respectively. The overall prevalence of elevated liver enzymes (ALT or AST), elevated FLI, and elevated FIB-4 scores were 38.4, 60.1, and 4.1%, respectively. The fully-adjusted prevalence ratios (95% CI) for elevated liver enzymes (either ALT or AST) and elevated FLI score comparing women to men were 2.99 (1.84—4.86) and 1.47 (1.18—1.84), respectively.
*Conclusions:* The prevalence of metabolic abnormalities and liver outcomes in this general population study was very high. The prevalence of metabolic and liver abnormalities was particularly high among women, an observation that could explain the atypical 1:1 male to female ratio of liver cancer in Guatemala.
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## Background

Non-alcoholic fatty liver disease (NAFLD), the most common form of chronic liver disease worldwide [1], affects around approximately 30% of the population in upper-income [1] and in some low- and middle-income countries [2,3]. NAFLD is strongly associated with obesity and incidence rates are expected to rise over time [4]. NAFLD is

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defined as the presence of hepatic steatosis in the setting of no significant alcohol consumption and the absence of other known causes [5]. NAFLD is not a benign condition, as it may progress to non-alcoholic steatohepatitis, liver fibrosis, and cirrhosis, and is associated with an increased risk of hepatocellular carcinoma [5], cardiovascular disease, diabetes, and all-cause mortality [6].

NAFLD affects all races and ethnic groups, but Hispanics have a particularly high prevalence, partly because of genetic susceptibility [7,8]. Although several studies have documented the burden of obesity and cardiometabolic disease in the Latin American region [9], NAFLD and liver disease have been generally overlooked. Only a few studies have documented the prevalence of NAFLD in this region, and these have been restricted either to specific age or ethnic specific groups, or have used hospital-based samples [10,11].

Guatemala is a low-middle income country in Central America experiencing a double burden of high rates of undernutrition and overweight/obesity. Recent studies conducted in urban and rural areas in Guatemala have documented a high prevalence of cardiometabolic risk factors [12,13], but there is no data on the prevalence of NAFLD. Of interest, Guatemala has the highest rate of liver cancer in the Western hemisphere with equal incidence among men and women, which is considered a very uncommon pattern [14]. Evaluating the distribution and predictors of NAFLD in Guatemala may thus provide insight into the factors driving the alarmingly high rates of liver cancer in this region, particularly considering that the prevalence of viral chronic hepatitis and heavy alcohol consumption are low [15–18]. Thus, the objective of this study was to describe, for the first time, the prevalence and distribution of NAFLD and its associated risk factors in a population-based sample of adults in Guatemala.

## Methods

### Study population

A cross-sectional study was conducted in men and women 40 years of age or older residing in urban and rural areas of Guatemala [18]. Study participants were recruited in five communities from different departments located in the Central and Western regions of Guatemala: Chichicastenango (Quiche department), Escuintla (Escuintla), Mixco (Guatemala), San Lucas Toliman (Solola), and San Pablo Jocopilas (Suchitepequez). Of the study sites, three were considered predominantly rural (Chichicastenango, San Pablo Jocopilas, and San Lucas Toliman) and two predominantly urban (Mixco and Escuintla). The communities were selected *ad hoc* based on a combination of representativeness, accessibility, and feasibility of conducting clinic-based visits. While site selection was not representative of the whole country, the sites identified were typical rural and urban communities in Guatemala.

Data collection was conducted between April and October 2016 in partnership with local clinics operated by the Ministry of Health and by non-government organizations in order to facilitate recruitment and referrals. Recruitment took place at the household level. In Mixco, households were selected at random from a formal sampling frame. In the other sites, study personnel selected households in the community using a non-probability sampling method. In each household, all adults aged 40 years and older who had no history of liver cancer and were able to provide informed consent were eligible. Up to two non-genetically-related participants per household were invited to participate.

A total of 677 households, which included 827 eligible individuals, were contacted; 461 participants gave written informed consent and ultimately 444 enrolled in the study. Participants with positive anti-HCV antibodies, HBsAg antigen, or anti-HBc antibodies, or who self-reported as current heavy drinkers defined as >7 drinks/week in women and >14 drinks/week in men (n = 20), and participants with missing data in relevant covariates (n = 13) were excluded from the analysis. The final number of participants included in the analysis was 411 (Fig. 1). Participants who were excluded from the analysis because of hepatitis B or C virus infection, current heavy drinking, or missing data, were more likely to be male but did not differ from included participants in age, residence, ethnicity, literacy, or family income (Appendix Table 1).

The study protocol and questionnaires were approved by the Institutional Review Boards (IRB) of the Johns Hopkins Bloomberg School of Public Health in Baltimore, MD, USA (IRB #6877) and the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala City, Guatemala (IRB #053-2015). All participants provided written informed consent. Informed consent was obtained in Spanish and translation services in Mayan languages (Kaqchikel and Quiche) were available upon request.

### Data collection

During the household visit, trained interviewers administered questionnaires previously used or validated by INCAP and the Pan-American Health Organization (PAHO). The questionnaires obtained information on demographic characteristics, education, health status, medical history, access to health care, medication use, physical activity, smoking, and alcohol intake. Ethnic background (indigenous or non-indigenous) was determined by participants' self-identification. Physical activity was assessed by using the International Physical Activity Questionnaire short form (IPAQ 6) [19]. Physical activity was categorized as inactive (no activity is reported or some activity but not enough to meet the upper categories), minimally active (≥3 days of vigorous activity of at least 20 min per day, or ≥5 days of moderate-intensity activity or walking for at least 30 min per day, or ≥5 days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-min/week) and active (vigorous–intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week or ≥7 days of any combination of walking, moderate-intensity or

| | Guatemala | Escuintla | Sololá | Suchitepéquez | Quiché | Total |
|---|---|---|---|---|---|---|
| Households Visited | 163 | 128 | 149 | 76 | 161 | 677 |
| Eligible Subjects | 144 | 166 | 202 | 115 | 200 | 827 |
| Informed consent | 85 | 93 | 98 | 84 | 101 | 461 |
| Enrolled | 82 | 90 | 90 | 82 | 100 | 444 |
| Complete data | 80 | 88 | 88 | 77 | 98 | 431 |
| Included | 76 | 82 | 85 | 72 | 96 | 411 |

**Figure 1** Flowchart of study participants by department.

vigorous intensity activities achieving a minimum of at least 3000 MET-minutes/week) [19]. Smoking status was categorized as never, former, and current. Alcohol intake was categorized as never, former, and current moderate ($\leq$7 drinks/week in women and $\leq$14 drinks/week in men). Subjects with current heavy intake ($>$7 drinks/week in women and $>$14 drinks/week in men) were excluded from the analysis (see exclusion criteria).

Upon completion of the household visit, participants were scheduled for a clinic visit within the same week. At the clinic visit, anthropometry and blood pressure were measured using standardized instruments and protocols. Height, weight and waist circumference were measured twice using calibrated scales (Seca mobile scale), stadiometers (Seca 213) and measuring tapes (Seca), and both measurements were averaged. A third measurement was taken if height measurements differed by $>$ 0.5 cm, weight measurements by $>$ 0.2 kg, or waist circumference measures by $>$ 0.5 cm, and then averaged the two closest measurements [20]. Body mass index (BMI) was calculated as weight in kg divided by height in m squared. Blood pressure was measured three times at 5-min intervals with the appropriate blood pressure cuff using automated Omron5 series sphygmomanometers, which have been validated according to the International Protocol of the European Society of Hypertension [21,22]. The second and third blood pressure measurements were averaged. If the difference between the second and third measurements was $>$10 mmHg, a fourth measurement was taken, and the last three measurements were averaged.

### Laboratory analyses

Blood samples were collected by a trained phlebotomist using a standard protocol. Participants were required to

fast for a minimum of 8 h prior to the clinic visit. A complete blood count (CBC) was analyzed on site within 2 h of extraction using a Nihon Kohden Celltac counter. All the remaining specimens were centrifuged, frozen ($-20$ °C) and shipped weekly to INCAP for analysis upon arrival.

Plasma glucose and serum total cholesterol, triglycerides, high-density lipoprotein cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (AST), and $\gamma$-glutamyl transferase (GGT) using a Cobas c111 analyzer (Roche Diagnostics). All laboratory analyses were performed according to equipment manufacturers' recommendations.

The presence of hepatitis B virus surface antigen (HBsAg), of hepatitis B core antibodies (anti-HBc) and hepatitis C virus antibodies (anti-HCV) were determined in the Hepatitis Diagnostic Laboratory of the University of Hannover Medical School in Germany as previously described [23].

### Study outcomes

The current study included metabolic outcomes and liver disease outcomes. Metabolic outcomes included obesity, central obesity, hypercholesterolemia, diabetes, and metabolic syndrome (MetS) and its components. Obesity was defined as a BMI $>$30 kg/m$^2$. Central obesity was defined as a waist circumference $\geq$90 cm in men and $\geq$80 cm in women based on cut-offs suggested by the International Diabetes Federation (IDF) [24]. Hypercholesterolemia was defined as a self-reported physician diagnosis, a self-reported use of lipid lowering medication, or a measured total cholesterol $>$200 mg/dl. Diabetes was defined as a self-reported physician diagnosis, a self-reported use of insulin or antidiabetic medication, or a measured fasting plasma glucose $\geq$126 mg/dl. MetS was

defined following IDF criteria [24,25] as the presence of central obesity plus two or more of the following measured abnormalities: serum triglycerides >150 mg/dl, HDL cholesterol <40 mg/dl in men or <50 mg/dl in women, blood pressure >130/85 mmHg, or serum glucose >100 mg/dl.

Liver disease outcomes included elevated liver enzymes, elevated Fatty Liver Index (FLI), and elevated FIB-4 score. The presence of elevated liver enzymes was defined as ALT >55 U/l in men and >31 U/l in women or AST >40 U/l in men and 25 U/l in women based on the cutoff values provided by the laboratory at INCAP. The presence of NAFLD was assessed using the Fatty Liver Index (FLI) [26–28], calculated as FLI = $100/(1 + e^{-X})$, where X = 0.953*ln (Triglycerides [mg/dl]) + 0.139*BMI [kg/m$^2$] + 0.718*ln (GGT [(U/l)]) + 0.053*Waist Circumference [cm] − 15.745. Elevated FLI was defined as a FLI >60 [27]. The FIB-4 score, a surrogate risk score for liver fibrosis [29], was also calculated as FIB-4 = (Age [years] * AST [U/l])/(Platelet Count [$10^9$/l] * ALT [U/l]$^{(1/2)}$). Elevated FIB-4 scores were defined as a FIB-4 score >2.67, a cutoff previously validated in patients with NAFLD [29].

### Statistical analysis

The objective of the analysis was to describe the overall prevalence of study outcomes and to compare their prevalence by sex, area of residence (urban vs. rural), and ethnicity (indigenous vs. non-indigenous). For bivariate comparisons, t-tests were used to assess differences in continuous variables and $\chi^{[2]}$ tests to assess differences in categorical variables. Poisson regression models were used to estimate adjusted prevalence ratios and 95% confidence intervals of study outcomes comparing women vs. men, indigenous vs. non-indigenous ethnicity, and rural vs. urban residence. Two models with progressive levels of adjustment were used. Model 1 was adjusted for age, sex, residence, and ethnicity. Model 2 was further adjusted for smoking, alcohol intake, and physical activity. A p-value <0.05 was considered statistically significant. Data analysis was conducted using Stata version 14 (StataCorp, College Station, TX, USA).

### Results

The mean age of study participants was 55.4 years (58.5 years in men, and 53.4 years in women; p < 0.001); 59.9% of study participants were women (Table 1). Over 38% of participants came from urban communities and 54.5% self-reported as indigenous. More than two-thirds (67.9%) of study participants had <6 years of formal education and 73.5% of participants reported a monthly income < US$ 400 per month (equivalent to the minimum wage in Guatemala). The prevalence of participants reporting current moderate alcohol consumption was 20.2%, and it was more common among men than among women (27.9 vs. 15.0%; p < 0.001). More than half (52.8%) of study participants were physically inactive. The prevalence of inactive participants was higher among women than men (63.4 vs. 37.0%; p < 0.001).

The overall prevalence of obesity, central obesity, diabetes, and MetS were 30.9, 74.3, 21.6, and 64.2%, respectively (Table 2). Compared to men, women had a higher prevalence of obesity (40.2 vs 17.0%, p < 0.001), central obesity (87.8 vs 54.3%, p < 0.001), low HDL (84.5 vs 77.0%, p 0.05), and MetS (76.4 vs 46.1%, p < 0.001). In fully-

| Characteristic | Overall (n = 411) | Women (n = 246) | Men (n = 165) | P value |
|---|---|---|---|---|
| **Age, years** | 55.4 (10.6) | 53.4 (9.75) | 58.5 (11.1) | <0.001 |
| **Age categories** | | | | <0.001 |
| 40–49 years | 144 (35.0) | 100 (40.7) | 44 (36.7) | |
| 50–59 years | 132 (32.1) | 84 (34.1) | 48 (29.1) | |
| >60 years | 135 (32.8) | 62 (25.2) | 73 (44.2) | |
| **Urban residence** | 158 (38.4) | 97 (39.4) | 61 (37.0) | 0.62 |
| **Indigenous ethnicity** | 224 (54.5) | 132 (53.7) | 92 (55.8) | 0.68 |
| **Illiterate** | 132 (32.1) | 97 (39.4) | 35 (21.2) | <0.001 |
| **Education < 6 years** | 279 (67.9) | 177 (72.0) | 102 (61.8) | 0.03 |
| **Family income < $400** | 302 (73.5) | 186 (75.6) | 116 (70.3) | 0.23 |
| **Smoking** | | | | <0.001 |
| Never | 238 (57.9) | 211 (85.8) | 27 (16.4) | |
| Former | 143 (34.8) | 32 (13.0) | 111 (67.3) | |
| Current | 30 (7.3) | 3 (1.2) | 27 (16.4) | |
| **Alcohol consumption** | | | | <0.001 |
| Never | 119 (28.9) | 113 (46.0) | 6 (3.6) | |
| Former | 209 (50.8) | 96 (39.0) | 113 (68.5) | |
| Current moderate | 83 (20.2) | 37 (15.0) | 46 (27.9) | |
| **Physical activity** | | | | <0.001 |
| Inactive | 217 (52.8) | 156 (63.4) | 61 (37.0) | |
| Minimally active | 140 (34.1) | 78 (31.7) | 62 (37.6) | |
| Active | 54 (13.1) | 12 (4.88) | 42 (25.4) | |

**Table 1** Characteristics of study participants.

Data presented are mean (SD) or number (%).

**Table 2** Prevalence ratios (95% confidence intervals) for metabolic abnormalities and liver disease outcomes comparing women to men.

| | Overall (n = 411) | Women (n = 246) | Men[a] (n = 165) | Model 1 | | Model 2 | |
|---|---|---|---|---|---|---|---|
| | Number (%) | Number (%) | Number (%) | Prevalence ratio (95% CI) | P-value | Prevalence ratio (95% CI) | P-value |
| **Metabolic abnormalities** | | | | | | | |
| Obesity | 127 (30.9) | 99 (40.2) | 28 (17.0) | 2.16 (1.49−3.11) | <0.001 | 2.83 (1.86−4.30) | <0.001 |
| Central obesity | 304 (74.3) | 215 (87.8) | 89 (54.3) | 1.61 (1.39−1.86) | <0.001 | 1.72 (1.46−2.02) | <0.001 |
| Hypercholesterolemia | 135 (32.8) | 85 (34.6) | 50 (30.3) | 1.14 (0.85−1.53) | 0.36 | 1.42 (0.95−2.11) | 0.08 |
| Low HDL | 335 (81.5) | 208 (84.5) | 127 (77.0) | 1.09 (0.98−1.20) | 0.09 | 1.18 (1.03−1.34) | 0.01 |
| Hypertriglyceridemia | 296 (72.0) | 173 (70.3) | 123 (74.5) | 0.92 (0.81−1.04) | 0.20 | 1.04 (0.88−1.22) | 0.59 |
| Diabetes | 89 (21.6) | 61 (24.8) | 28 (17.0) | 1.43 (0.97−2.11) | 0.07 | 1.53 (0.88−2.65) | 0.13 |
| Metabolic Syndrome | 264 (64.2) | 188 (76.4) | 76 (46.1) | 1.62 (1.36−1.94) | <0.001 | 1.87 (1.53−2.29) | <0.001 |
| **Liver disease outcomes** | | | | | | | |
| Elevated AST | 154 (37.5) | 131 (53.2) | 23 (13.9) | 3.77 (2.52−5.64) | <0.001 | 2.74 (1.67−4.48) | <0.001 |
| Elevated ALT | 100 (24.3) | 91 (37.0) | 9 (5.4) | 6.52 (3.37−12.61) | <0.001 | 5.69 (2.60−12.46) | <0.001 |
| Elevated ALT or AST | 158 (38.4) | 135 (54.9) | 23 (13.9) | 3.89 (2.60−5.81) | <0.001 | 2.99 (1.84−4.86) | <0.001 |
| Elevated FLI score | 246 (60.1) | 163 (66.5) | 83 (50.6) | 1.25 (1.05−1.49) | 0.009 | 1.47 (1.18−1.84) | <0.001 |
| Elevated FIB-4 score | 17 (4.1) | 9 (3.7) | 8 (4.8) | 1.01 (0.41−2.44) | 0.99 | 0.39 (0.12−1.20) | 0.10 |

Model. 1, adjusted for age group, ethnicity, and residence. Model 2, further adjusted for smoking, alcohol intake, and physical activity.
[a] Reference category.

adjusted models, the prevalence ratios (95% CI) for obesity, central obesity, low HDL, and MetS comparing women to men were 2.83 (1.86−4.30), 1.72 (1.46−2.02), 1.18 (1.03−1.34), and 1.87 (1.53−2.29), respectively.

The overall prevalence of elevated liver enzymes (ALT or AST), elevated FLI, and elevated FIB-4 scores were 38.4, 60.1, and 4.1%, respectively (Table 2). Compared to men, women had a higher prevalence of elevated liver enzymes (54.9 vs 13.9%, p < 0.001) and elevated FLI score (66.5 vs 50.6%, p < 0.001). In fully-adjusted models, the prevalence ratios (95% CI) for elevated liver enzymes (either ALT or AST) and elevated FLI score comparing women to men were 2.99 (1.84−4.86) and 1.47 (1.18−1.84), respectively.

When stratifying the results by ethnicity (Table 3), participants who self-identified as indigenous generally had a lower prevalence of metabolic abnormalities. In fully-adjusted models, the prevalence ratios (95% CI) for central obesity and hypercholesterolemia comparing indigenous to non-indigenous participants were 0.79 (0.68−0.92) and 0.57 (0.39−0.82), respectively. Indigenous participants had also generally lower prevalence of liver disease markers than non-indigenous participants, but the differences were not statistically significant. No significant differences were observed in metabolic abnormalities or in liver disease outcomes when participants were stratified by rural vs. urban residence (Table 4).

**Table 3** Prevalence ratios (95% confidence intervals) for metabolic abnormalities and liver disease outcomes comparing indigenous to non-indigenous participants.

| Characteristic | Indigenous (n = 224) | Non-Indigenous[a] (n = 187) | Model 1 | | Model 2 | |
|---|---|---|---|---|---|---|
| | Number (%) | Number (%) | Prevalence ratio (95% CI) | P-value | Prevalence ratio (95% CI) | P-value |
| **Metabolic abnormalities** | | | | | | |
| Obesity | 56 (25.0) | 71 (38.0) | 0.80 (0.53−1.20) | 0.29 | 0.86 (0.57−1.30) | 0.49 |
| Central obesity | 144 (64.6) | 160 (86.0) | 0.79 (0.68−0.92) | 0.003 | 0.79 (0.68−0.92) | 0.004 |
| Hypercholesterolemia | 55 (24.6) | 80 (42.8) | 0.56 (0.39−0.81) | 0.002 | 0.57 (0.39−0.82) | 0.003 |
| Low HDL | 186 (83.0) | 149 (79.7) | 1.03 (0.91−1.17) | 0.56 | 1.03 (0.91−1.17) | 0.61 |
| Hypertriglyceridemia | 158 (70.5) | 138 (73.8) | 0.97 (0.82−1.14) | 0.76 | 0.97 (0.82−1.14) | 0.74 |
| Diabetes | 35 (15.6) | 54 (28.8) | 0.83 (0.45−1.52) | 0.55 | 0.84 (0.45−1.59) | 0.61 |
| Metabolic Syndrome | 124 (55.4) | 140 (74.8) | 0.81 (0.66−1.00) | 0.06 | 0.82 (0.66−1.01) | 0.06 |
| **Liver disease outcomes** | | | | | | |
| Elevated AST | 82 (36.6) | 72 (38.5) | 0.96 (0.68−1.37) | 0.85 | 0.93 (0.66−1.32) | 0.70 |
| Elevated ALT | 55 (24.6) | 45 (24.1) | 1.01 (0.64−1.60) | 0.94 | 1.02 (0.65−1.62) | 0.92 |
| Elevated ALT or AST | 85 (37.9) | 73 (39.0) | 0.98 (0.70−1.39) | 0.95 | 0.96 (0.69−1.35) | 0.83 |
| Elevated FLI score | 113 (50.7) | 133 (71.5) | 0.82 (0.64−1.04) | 0.12 | 0.84 (0.65−1.07) | 0.15 |
| Elevated FIB-4 score | 7 (3.1) | 10 (5.3) | 0.42 (0.14−1.21) | 0.11 | 0.40 (0.14−1.16) | 0.09 |

Model 1, adjusted for age group, sex, and residence. Model 2, further adjusted for smoking, alcohol intake, and physical activity.
[a] Reference category.

**Table 4** Prevalence ratios (95% confidence intervals) for metabolic abnormalities and liver disease outcomes comparing rural to urban participants.

| Characteristic | Rural (n = 253) | Urban[a] (n = 158) | Model 1 | | Model 2 | |
|---|---|---|---|---|---|---|
| | Number (%) | Number (%) | Prevalence ratio (95% CI) | P-value | Prevalence ratio (95% CI) | P-value |
| **Metabolic abnormalities** | | | | | | |
| Obesity | 65 (25.7) | 62 (39.2) | 0.77 (0.52−1.15) | 0.20 | 0.80 (0.53−1.21) | 0.30 |
| Central obesity | 168 (66.9) | 136 (86.1) | 0.94 (0.81−1.09) | 0.41 | 0.96 (0.83−1.11) | 0.60 |
| Hypercholesterolemia | 70 (27.7) | 65 (41.1) | 1.03 (0.73−1.46) | 0.86 | 1.04 (0.74−1.48) | 0.80 |
| Low HDL | 209 (82.6) | 126 (79.7) | 1.01 (0.89−1.15) | 0.82 | 1.01 (0.89−1.16) | 0.77 |
| Hypertriglyceridemia | 179 (70.7) | 117 (74.0) | 0.96 (0.82−1.14) | 0.71 | 0.97 (0.83−1.15) | 0.78 |
| Diabetes | 39 (15.4) | 50 (31.6) | 0.58 (0.32−1.06) | 0.08 | 0.62 (0.33−1.17) | 0.14 |
| Metabolic Syndrome | 144 (56.9) | 120 (75.9) | 0.89 (0.72−1.08) | 0.26 | 0.92 (0.75−1.12) | 0.40 |
| **Liver disease outcomes** | | | | | | |
| Elevated AST | 93 (36.7) | 61 (38.6) | 1.03 (0.72−1.47) | 0.86 | 1.00 (0.71−1.42) | 0.99 |
| Elevated ALT | 62 (24.5) | 38 (24.0) | 1.05 (0.65−1.69) | 0.82 | 1.05 (0.65−1.69) | 0.83 |
| Elevated ALT or AST | 96 (37.9) | 62 (39.2) | 1.03 (0.73−1.46) | 0.87 | 1.01 (0.72−1.42) | 0.94 |
| Elevated FLI score | 130 (51.8) | 116 (73.4) | 0.82 (0.65−1.03) | 0.09 | 0.83 (0.66−1.06) | 0.13 |
| Elevated FIB-4 score | 10 (3.9) | 7 (4.4) | 1.77 (0.63−4.97) | 0.28 | 1.54 (0.57−4.15) | 0.40 |

Model 1, adjusted for age group, sex, and ethnicity. Model 2, further adjusted for smoking, alcohol intake, and physical activity.

[a] Reference category.

## Discussion

Using a series of non-invasive surrogate markers in adults above 40 years of age living in urban and rural areas of Guatemala, the present study showed high prevalences of all metabolic abnormalities that were studied: 74.3% for central obesity, 21.6% for diabetes, and 64.2% for MetS. Approximately 60% of participants had an elevated FLI score, a surrogate marker for fatty liver disease, 38.4% had unexplained elevated liver enzymes, and 4.1% had elevated FIB-4 score, a surrogate marker for liver fibrosis. The prevalence of metabolic and liver abnormalities was particularly high among women, a difference that could underlie the unusual 1:1 male to female ratio of liver cancer in this population [18]. Metabolic abnormalities were also more common in non-indigenous participants. The high prevalence of metabolic and liver abnormalities is a major public issue given their strong association with long-term morbidity and mortality.

There are no prior estimates of the burden of NAFLD in Guatemala or among indigenous individuals in the region. Studies conducted in the US have consistently documented large disparities in the prevalence of NAFLD by race/ethnicity, with Hispanics being disproportionally affected [1,8,30,31]. Compared to other race/ethnicity groups, Hispanics have also a higher prevalence of cirrhosis and higher liver-related mortality [32] and while chronic liver disease and cirrhosis are the 13th leading cause of death in the US general population, they are the 6th leading cause of death among Hispanics [33].

Among Hispanics residing in the US, it has been further documented that the prevalence of NAFLD varies by Hispanic/Latino background, with a higher prevalence among those of Mexican and Central American background compared to the other groups [34,35]. Previous studies in Mexico reported a wide variation in prevalence, ranging from 15% in a small sample to 82% in a sample of hospitalized patients [11]. In Colombia, Chile and Brazil, estimates ranged between 17 and 23% [10,11,36]. The prevalence of NAFLD in the current study was higher than in most other studies in Hispanic/Latino populations, but these studies are difficult to compare due to differences in study design, population characteristics, and outcome definition.

The reasons for the increased rates of NAFLD among Hispanics in the US compared to other race/ethnicities are not fully understood, but may include a combination of environmental factors, genetic susceptibility [37−39] and poor access to preventive and curative health services [40]. Obesity and insulin resistance are the most important risk factors driving the high prevalence of NAFLD and metabolic abnormalities worldwide. The high prevalence of obesity and metabolic abnormalities in the current study and their increased prevalence in women compared to men are consistent with estimates from recent studies conducted in other settings in Guatemala. In national surveys, the prevalence of overweight and obesity in women 15−49 years of age has increased steadily from 34.2% in 1995 to 51.9% in 2015 [41]. In 2008, the prevalence of overweight and obesity among those 15−59 years of age was 35.8% in men and 49.4% in women, and the prevalence of obesity was almost half in men compared to women (9.9 vs 17.0%) [42].

The reasons for gender differences in metabolic abnormalities and liver disease are likely complex. In younger women, high estrogen levels have multiple beneficial metabolic effects, including a reduction of the risk of fatty liver by partitioning fatty acids towards

production of ketone bodies instead of very low-density lipoprotein triacilgycerols [43,44]. This metabolic advantage is lost after menopause. In our study, differences in physical activity may also contribute to the higher prevalence of metabolic abnormalities in women compared to men. In a national survey, more men than women reported walking $\geq 2$ h/day (48.4 vs 37.3%) [42]. These differences may be more marked in rural regions, as rural men are more likely to be dedicated to physically demanding occupations [45].

Similar patterns of greater cardiometabolic risk in women compared men have also been observed in other studies in Central America. In a study of parents of school-aged children in nine Mesoamerican cities, Guatemalan women had a higher prevalence of MetS than Guatemalan men (45.2 vs 30.0%, respectively) [46]. In addition, a birth-cohort study in rural Guatemala that followed participants for almost 50 years showed that, by young adulthood (25−42 years of age), women had a much higher prevalence of obesity, diabetes, and MetS compared to men [47].

As in other countries in Latin American, low income and low levels of education may underlie the obesity epidemic in the region [45]. This may be explained in part by a staple diet based on corn products among low and by an increasing supply of cheap processed foods. In the current analysis, indigenous participants had a lower prevalence of metabolic abnormalities compared to indigenous participants, and these differences persisted after adjusting for residence and physical activity levels. Additional studies are needed to understand the socioeconomic determinants of metabolic abnormalities in Guatemala and other Central American countries.

Several limitations to this study must be acknowledged. First, the cross-sectional design used was susceptible to selection bias due to the lack of a formal sampling frame for study participants (except for participants in Mixco) and to the presence of non-response. However, the estimates in Mixco, the study center that used a representative sampling frame, were similar to those from other centers (data not shown).

Second, information on alcohol intake was obtained by self-report, which may result in an underestimation of alcohol consumption. In addition, information on physical activity was obtained using IPAQ 6 [19]. Although the IPAQ-6 has been validated in many populations (including Guatemala [19]) and continues to be regarded as an adequate tool for population studies, we cannot discard the possibility that its use may introduced bias in the assessment of physical activity in our study sample. We notice, however, that the information collected by the IPAQ-6 is not restricted to walking, but it also includes other activities of varying degrees of intensity. Furthermore, the gender differences in physical activity observed in our data are consistent with those reported in previous studies in urban and rural areas of Guatemala using other instruments to assess physical activity [12,48].

Third, liver enzymes and two related non-invasive risk scores, the FLI and FIB-4, were used to define fatty and liver fibrosis, respectively. The FLI was developed in a small Italian sample [27], and although it has been validated in other populations, its accuracy among Hispanics is unknown. The FIB-4 score was developed for the detection of liver fibrosis among patients with viral hepatitis, but has been externally validated among Hispanics/Latinos and demonstrated an area under the curve of 0.74 for the detection of advance fibrosis [49]. Given the large burden of NAFLD among Hispanics/Latino populations, and the need for non-invasive means to assess the presence of the disease, future studies are needed to further validate their use in these settings. In addition, future studies with imaging methods such as ultrasound or ultrasound elastography will help provide a more accurate characterization of the burden of NAFLD and liver fibrosis in urban and rural samples in Central America.

Finally, a diagnosis of NAFLD was established in the current study as the presence of fatty liver in participants without chronic viral hepatitis infection and without heavy alcohol consumption, but other less common causes of fatty liver, such as iron overload or the use of hepatotoxic drugs, were not excluded.

In summary, the current study identified a very high prevalence of obesity, metabolic abnormalities, diabetes, NAFLD, and elevated liver enzymes in a general population study conducted in urban and rural areas in Guatemala. There is already widespread concern on the long-term consequences of diabetes and other metabolic abnormalities, but NAFLD is also associated with multiple adverse long-term consequences, including progression to advanced liver disease, cirrhosis, liver cancer, subclinical myocardial injury and increased cardiovascular risk, inflammation, and chronic kidney disease [5,6,50−56]. The high prevalence of metabolic abnormalities and liver disease in Guatemala is a major public health concern and a burden to development in a low-income country. Furthermore, the prevalence of metabolic and liver abnormalities is particularly high among women, an observation that could explain the atypical 1:1 male to female ratio of liver cancer in Guatemala. Further research using representative samples and non-invasive liver imaging techniques are needed to confirm these findings and to identify the causes and potential solutions to the very high prevalence of metabolic abnormalities, NAFLD, and unexplained elevated liver enzymes in Guatemala.

## Acknowledgement

**Appendix Table 1. Demographic characteristics of included and excluded participants.**

| Characteristic | Included | | | Excluded | | |
|---|---|---|---|---|---|---|
| | Overall (n = 411) | Women (n = 246) | Men (n = 165) | Overall (n = 50) | Women (n = 16) | Men (n = 34) |
| **Age, years** | 55.4 (10.6) | 53.4 (9.75) | 58.5 (11.1) | 55.12 (11.6) | 54.6 (10.8) | 55.3 (12.3) |
| **Age categories** | | | | | | |
| 40−49 years | 144 (35.0) | 100 (40.7) | 44 (36.7) | 19 (38.0) | 6 (37.5) | 13 (38.2) |
| 50−59 years | 132 (32.1) | 84 (34.1) | 48 (29.1) | 14 (28.0) | 4 (25.0) | 10 (29.4) |
| >60 years | 135 (32.8) | 62 (25.2) | 73 (44.2) | 17 (34.0) | 6 (37.50) | 11 (32.3) |
| **Male** | 165 (40.1) | − | − | 34 (68.0)* | − | − |
| **Urban residence** | 158 (38.4) | 97 (39.4) | 61 (37.0) | 19 (38.0) | 5 (31.2) | 14 (41.2) |
| **Indigenous ethnicity** | 224 (54.5) | 132 (53.7) | 92 (55.8) | 26 (52.0) | 9 (56.2) | 17 (50.0) |
| **Illiterate** | 132 (32.1) | 97 (39.4) | 35 (21.2) | 13 (26.0) | 4 (25.0) | 9 (26.5) |
| **Family income < $400** | 302 (73.5) | 186 (75.6) | 116 (70.3) | 42 (84.0) | (81.3) | 29 (85.3) |

Data presented are mean (SD) or number (%).
*p-value <0.05 for the $\chi^{[2]}$ test or Fisher exact test between included vs excluded.

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