Title

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Journal

Journal of digestive diseases, 17(5)

ISSN

1751-2972

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Publication Date

2016-05-01

DOI

10.1111/1751-2980.12341

Peer reviewed

HHS Public Access

Author manuscript

J Dig Dis. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

J Dig Dis. 2016 May ; 17(5): 304–312. doi:10.1111/1751-2980.12341.

Longitudinal association of obesity, metabolic syndrome and diabetes with risk of elevated aminotransferase levels in a cohort of Mexican health workers

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INTRODUCTION

Mexico has been experiencing an epidemiological shift in recent years with a drastic increase in rates of non-communicable diseases throughout the country.[1,2] Cirrhosis and other chronic liver diseases (CLD) were the fifth leading cause of general mortality in 2013, representing 7.2% of male deaths and 3.4% of female deaths in Mexico.[3] In 2008, CLD was the second leading cause of death among Mexicans between the ages of 15 and 64.[4] Estimates indicate that by 2050, up to 90% of CLD cases in Mexico will be attributable to obesity and alcohol consumption[5], as compared to other countries or populations that have higher rates of liver disease due to infection with hepatitis B (HBV) or hepatitis C (HCV). CLD is a major public health issue in more developed countries such as the United Kingdom, where liver disease is also the fifth most common cause of death. Unlike other causes of mortality around the world, liver disease death rates are increasing rather than declining.[6]

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Infection with HBV or HCV and alcohol consumption are well established risk factors for CLD.[7,8] Other risk factors include obesity[9,10], metabolic syndrome[11,12], and diabetes[10,13,14], and the proposed mechanism is through the development of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).[10,15,16] Rates of CLD have been increasing along with the rapidly growing prevalence of obesity, metabolic syndrome, and diabetes in Mexico. In 2010, approximately 68% of men and 74% of women in Mexico were overweight or obese, and these numbers are predicted to rise to 88% and 91%, respectively by 2050.[17] The prevalence of metabolic syndrome is estimated to be as high as 40% among Mexican adults, who have an increased susceptibility of developing it, as compared to other Latino populations.[18] Diabetes was the second major cause of mortality in 2013[3], and Mexico has one of the highest type 2 diabetes incidence rates in the world.[19] A better understanding of these specific risk factors is imperative in order to implement more effective strategies to deal with the two million cases of CLD that are projected to occur in Mexico by 2050.[5]

Alanine aminotransferase (ALT) levels are commonly used as clinical indicators of liver health. Common causes of elevated ALT include consuming alcohol in excess, HBV, HCV, as well as the presence of NAFLD or NASH.[20] The specific reasons for elevated ALT levels differ greatly depending on the population being studied; however, regardless of etiology, elevated ALT levels have consistently been associated with liver disease.[21,22] Although not all people with elevated ALT levels have or will develop liver disease, this measure is widely accepted as a surrogate for asymptomatic liver disease.[23] Studies suggest that more advanced liver disease and cirrhosis can be identified from slight aminotransferase elevations, and that elevated aminotransferase levels are more common among Latinos.[24–26]

Most reports of the major risk factors for CLD come from cross-sectional studies.[26–28] Few longitudinal studies have examined the impact of specific risk factors on the development of CLD over time.[29–32] For this study, we aimed to investigate the association between known risk factors and the development of incident elevated ALT levels, in a cohort of Mexican adults. We examined clinical and questionnaire data that was collected as part of a cohort study of adult Mexican health workers. We hypothesized that participants who acquired or maintained certain risk factors during the study period would have a higher risk of elevated ALT levels than those who did not. We tested this hypothesis by examining the cross-sectional and longitudinal associations between gender, age, body mass index (BMI), diabetes, and metabolic syndrome, and risk of elevated ALT levels, controlling for potential confounders.

METHODS

Study Design and Population

Data were obtained from the Mexican Health Worker Cohort Study (MHWCS), a longitudinal study of workers and their immediate family members, from two large health care institutions in Cuernavaca, Mexico: the Mexican Institute of Social Security (IMSS) and the National Institute of Public Health (INSP). The MHWCS collects information from physical examinations, self-reported questionnaires, and laboratory tests, to prospectively evaluate risk factors and incidence of chronic disease. From 2004–2006 (Wave 1), nearly

4,000 health workers enrolled in the MHWCS; and during 2011–2013 (Wave 2), a total of 1,855 participants were followed-up. Informed consent was obtained from all participants. Further details regarding the design and methods of the MHWCS can be found elsewhere.[33–35]

Of the 1,855 participants who were followed-up, we excluded those who had incomplete information on ALT, BMI, education status, diabetes, metabolic syndrome, or alcohol consumption, or were under 20 years old in Wave 1 (n= 319). An additional 74 participants were excluded because they had HBV or HCV, cirrhosis, or had inconsistencies regarding their diabetes status. The final sample consisted of 1,462 participants over the age of 20 with complete questionnaire and laboratory data from Wave 1 and Wave 2. Although only 38% of the 3,877 participants from Wave 1 were followed up in Wave 2 and included as part of this study, we found no statistically significant differences in age, sex, education status, BMI, prevalence of diabetes or metabolic syndrome, and alcohol consumption between the two groups. (Data not shown)

Definition of Independent Variables

Body Mass Index—Participants were classified according to BMI (kg/m^2) based on the recommendations of the National Heart, Lung, and Blood institute: normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2).[36]

Diabetes—Type 2 diabetes was defined for men and women as having any of the following: a medical history of diabetes (excluding during pregnancy), currently taking diabetes medication, a plasma glucose level >125 mg/dL after fasting 12 hours, or a random glucose test >200 mg/dL.[37]

Metabolic syndrome—We used the definition developed by the National Cholesterol Education Program's Adult Treatment Panel III (ATP III), which is having three or more of the following criteria: (1) waist circumference ≥88 cm for women and ≥102 cm for men; (2) triglycerides ≥150 mg/dl; (3) HDL-cholesterol <50 mg/dL for women and <40 mg/dL for men; (4) a systolic blood pressure ≥130 mg Hg, diastolic blood pressure ≥85 mg Hg, blood pressure ≥130/85 mmHg, or currently taking blood pressure medication; and (5) a fasting glucose ≥110 mg/dL.[38]

Alcohol Consumption—Participants were categorized as either non-drinker/moderate drinker or heavy/binge drinker based on the Centers for Disease Control (CDC) definitions. Moderate drinkers were defined as having one or fewer drinks per day for women and two or fewer drinks per day for men. Heavy drinking was defined as 2–4 drinks per day for women, and 3–4 drinks per day for men. Binge drinking was defined as having five or more drinks at one time for both men and women.[39]

Definition of Dependent Variable

The main dependent variable in this study is alanine aminotransferase (ALT) level, which was classified as elevated when ALT >40 IU/L for both men and women.[25,26,40] ALT levels were determined from blood samples obtained from participants after fasting 12 for hours.

The blood samples were sent to the IMSS Regional Hospital laboratory after they were centrifuged and frozen at −20° C. ALT levels were determined by the catalytic concentration from the rate of decrease of nicotinamide adenine dinucleotide measured at 340 nm by means of a lactate dehydrogenase coupled reaction.[41,42]

Statistical Analysis

Chi-square tests were used to examine the unadjusted cross-sectional association of each risk factor with elevated ALT at each wave. Multivariable logistic regression models were used to calculate unadjusted and adjusted odds ratios and 95% confidence intervals for the cross-sectional associations, in Wave 1 (W1) and Wave 2 (W2) separately. The models progressively adjusted for age, sex and BMI, then additionally for alcohol use and education.

Longitudinal analyses were conducted for participants who had normal ALT levels in W1 (n=1,217), to examine the association of changing risk factor status over time with development of an incident elevated ALT result at W2. We used multivariable logistic regression to compute unadjusted and adjusted odds ratios and 95% confidence intervals. BMI status over time was categorized into five groups: *remained normal*: (normal (W1) to normal (W2)); *weight loss*: (obese (W1) to overweight (W2), obese (W1) to normal (W2), or overweight (W1) to normal (W2)); *remained overweight* (overweight (W1) to overweight (W2), *remained obese* (obese (W1) to obese (W2); or *weight gain* (normal (W1) to overweight (W2), normal (W1) to obese (W2), or overweight (W1) to obese (W2)). Diabetes status was categorized into three groups: *never diabetic* (not diabetic (W1) to not diabetic (W2)); *remained diabetic* (diabetic (W1) to diabetic (W2)); and *developed diabetes* (not diabetic (W1) to diabetic (W2)). Metabolic syndrome status over time was classified the same way as diabetes, with the additional category of *no longer having metabolic syndrome* (metabolic syndrome present (W1) to not present (W2)). Logistic regressions were examined using the following models: (1) unadjusted; (2) adjusting for sex, age, and BMI; and (3) adjusting for sex, age, BMI, education status, and alcohol consumption. All statistical analyses were conducted using Stata 12.[43] For all analyses, a two-sided p-value <0.05 was considered statistically significant

RESULTS

Table 1 reports the socio-demographic characteristics of the sample and compares the prevalence of elevated ALT by risk factor in Wave 1 and Wave 2. In both Wave 1 and Wave 2, the prevalence of elevated ALT was greater among men than women. In Wave 1, the prevalence of elevated ALT among men was more than double (29%) what was observed among women (13%). Individuals over 60 were at lower risk of having elevated ALT than those under 60, but the prevalence of elevated ALT did not differ greatly by education status. With respect to BMI, obese individuals were more than four times as likely to have elevated ALT compared to normal weight (33% vs. 7%), and overweight individuals were almost three times more likely to have elevated ALT than those who were normal weight (18% vs. 7%). Diabetics in Wave 1 were almost twice as likely to have elevated ALT levels as compared to non-diabetics (16% vs. 31%), and a similar pattern was observed with

metabolic syndrome and alcohol consumption (13% vs. 26% and 14% vs. 28%, respectively). (Table 1)

The cross-sectional analyses of risk factors for elevated ALT levels for Wave 1 and Wave 2 are presented in Table 2. Three models were fit to examine the association between risk of elevated ALT levels and specific demographic and risk factor variables when progressively adjusting for potential confounders (Model 1: unadjusted; 2: adjusted for sex, age, and BMI; and 3: additionally adjusted for education status, and alcohol consumption). In the fully adjusted Model 3 for Wave 1, males had a greater than two-fold odds of elevated ALT than females (OR= 2.3, 95% CI: 1.7–3.2). Overweight participants had nearly three times higher odds of elevated ALT levels as compared to those who were normal weight, and obese participants had a 6.6 higher odds than normal weight participants. Being diabetic (OR= 2.1, 95% CI 1.3–3.5) and having metabolic syndrome (OR=1.7, 95% CI 1.2–2.3) were also significantly associated with elevated ALT levels in Wave 1. Heavy/Binge alcohol consumption was not significantly associated with elevated ALT after adjusting for potential confounders. The results for Wave 2 were generally similar to the results for Wave 1. Neither metabolic syndrome nor heavy/binge drinking were associated with elevated ALT in the Wave 2 fully adjusted Model 3.

Table 3 shows the longitudinal analysis of the association between change in risk factor status from Wave 1 to Wave 2, and odds of having elevated ALT levels in Wave 2 among participants with normal ALT levels in Wave 1. The same three models that were used for Table 2 are presented, with a focus on the results of Model 3 (adjusted for sex, age, BMI, education status, and alcohol consumption). The increased risk of elevated ALT that was observed among males in the cross-sectional analyses (Table 2), was not evident in the longitudinal analyses (OR= 1.3, 95% CI 0.8–2.2). Participants under the age of 60 at Wave 1 had a more than three times greater odds of developing elevated ALT from Wave 1 to Wave 2, as compared to older participants. Individuals who remained overweight or obese from Wave 1 to Wave 2 also had an increased risk of elevated ALT (OR=2.5 and OR= 3.1 respectively), compared to participants who remained at a normal weight over time. The category with the greatest risk of incident elevated ALT levels was weight gain that resulted in a change in BMI status (normal to overweight, normal to obese, or overweight to obese) (OR= 4.1, 95% CI 2.2–7.6), as compared to those who remained at a normal weight from Wave 1 to Wave 2. Participants who developed diabetes had a nearly three-fold higher odds of having elevated ALT levels in Wave 2, compared to those who did not have diabetes at either time period (OR=2.7, 95% CI 1.3–5.4). Individuals who developed metabolic syndrome, as well as those who had metabolic syndrome that resolved by Wave 2, were at increased risk of elevated ALT levels (OR= 2.2 for both), compared to those who never had metabolic syndrome.

DISCUSSION

This study examined the cross-sectional and longitudinal association between elevated ALT and specific risk factors in a cohort of Mexican adults. The results of our study indicate that remaining overweight or obese, weight gain over time that results in a BMI category, as well as the presence of diabetes or metabolic syndrome, are associated with a greater risk of

having incident elevated ALT levels. These findings are consistent with other studies that have investigated the prevalence and predictors of elevated aminotransferase activity as a potential surrogate for NAFLD among adults.[24–26,44] Our findings also confirmed the hypothesis that those who acquired or maintained certain risk factors during the study period would have a higher risk of elevated ALT levels than those who did not.

Elevated ALT levels were observed among approximately 17% of the study sample in Wave 1 and 15% in Wave 2. These findings are comparable to the 16% prevalence of elevated ALT found among a representative sample of U.S. Latino adults from the 2005–2008 National Health and Nutrition Examination Survey (NHANES).[45] This study also reported a prevalence of elevated ALT of 6% and 9% among non-hispanic blacks and non-hispanic whites, respectively. However, unlike our study which used a cut point of ALT >40 IU/L for both men and women, Tsai et al. used a higher cut point for men (ALT > 47 IU/L) and a lower cut point for women (ALT > 30 IU/L).[45] Consistent with previous studies, our cross-sectional findings also indicate that males have a significantly greater risk of elevated ALT levels, as do individuals who are under the age of sixty.[26,46–48]

The cross-sectional association between obesity and elevated ALT levels is well established in the literature.[22,24,25,46] However, to the best of our knowledge, this is the first study that examined how change in BMI status over time affects risk of elevated ALT in a cohort of Mexican adults. We observed a greater than 2.5-fold increased odds of elevated ALT among overweight individuals in both waves, which rose to an over four-fold risk if they were obese. These results are similar to those found by Flores et al., who reported an OR of 2.5 for overweight and an OR of 6.07 for obese Mexican-American adults who participated in NHANES IV. These results were higher than the ORs observed among their non-hispanic black and white counterparts, although the rates of obesity and diabetes are similar between the groups.[26]

A critical finding of this study is that weight gain over time that results in a BMI category change puts individuals at an increased risk of having elevated ALT levels as compared to those who remain at a normal BMI over time. Weight gain over time that did not result in a BMI category change was not significantly associated with an increased risk of elevated ALT (results not shown), which suggests that substantial weight gain is a more important risk factor. Participants who remained overweight or obese from Wave 1 to Wave 2 were found to have a 2.5 and 3.1 higher odds of elevated ALT, respectively, as compared to participants who maintained a normal weight. Surprisingly, even the overweight and obese participants who lost weight and changed to a lower BMI category from Wave 1 to Wave 2 were observed to have an increased risk of elevated ALT levels, although this was not a statistically significant association, perhaps due to small sample size.

We observed a prevalence of elevated ALT of 16% and 13% among non-diabetics and 31% and 22% among diabetics in Waves 1 and 2, respectively. Our cross-sectional analyses indicate twice the odds of elevated ALT levels among diabetics as compared to non-diabetics. Individuals with normal ALT levels who developed diabetes between Wave 1 and Wave 2 had a greater risk of developing elevated ALT than those who remained diabetic, which suggests that more recently diagnosed diabetes patients may have a higher risk of

elevated ALT levels than those who have had the disease for a longer period of time. Our study focused on the association between acquiring diabetes over time and risk of elevated ALT levels, but a recent meta-analysis reports that ALT levels also exhibit a dose-response effect on risk of type-2 diabetes, which increases by approximately 20% for every 5-IU/L increase in ALT levels.[49] Diabetes has also been shown to be associated with a two- to three-fold increase in risk of liver cancer, regardless of what other major risk factors are present.[14] Diabetes is currently the second leading cause of death in Mexico[3], and an estimated 12 million cumulative incident cases of type-2 diabetes are expected by 2050.[19] Based on our findings and those of other studies, the increasing rates of diabetes in Mexico are likely to result in much higher rates of CLD.

Elevated levels of ALT were observed among 13% and 14% of participants without metabolic syndrome and among 26% and 20% of those with metabolic syndrome in Waves 1 and 2 of our study, respectively. Our findings are comparable to those of a population-based study of Latinos in the U.S., which reported a prevalence of elevated ALT of 19% among those with metabolic syndrome.[46] Our longitudinal results indicate that individuals who acquire metabolic syndrome, as compared to those who had it throughout the study period, had a higher risk of developing elevated ALT. We also found a significantly increased risk for those who had metabolic syndrome in Wave 1 but no longer had it in Wave 2. Although we expected that resolution of metabolic syndrome would have been associated with a lower risk of elevated ALT, this result may indicate that even a past diagnosis of metabolic syndrome increases risk of future elevated ALT.

This study has some limitations. The MHWCS is not a population-based sample and is not representative of the Mexican population. Participants are mostly health workers who are likely to be healthier and more educated than the general population. The sample was also predominantly female. The MHWCS participants may be considered representative of middle-income adults who reside in urban areas of central Mexico, which accounts for approximately 34% of the population.[50] Other limitations include inadequate alcohol consumption data in Wave 2, small sample sizes for individuals who resolved metabolic syndrome or lost weight between Wave 1 and 2, and the fact that we only had data for two time points. Additionally, less than 40% of the 3,877 participants from Wave 1 were included as part of this study, but we found no statistically significant differences between these two groups. Despite these limitations, this is the first study to report the association over time between elevated ALT and established risk factors, such as obesity, diabetes, and metabolic syndrome in a cohort of Mexican adults.

To the extent that elevated ALT activity may reflect underlying liver disease such as NAFLD[51], our findings indicate that a significant number of Mexicans are at increased risk of developing CLD due to the high rates of obesity, diabetes and metabolic syndrome in this population. Interventions to reduce obesity and some of its health related consequences, including diabetes and metabolic syndrome, should be a public health priority in Mexico. CLD has also been shown to disproportionately affect Latinos in the U.S.[52,53] The implications of our study results are relevant not only to Mexico, but also to the U.S., where the risk of elevated ALT is greater among the Mexican-American population, due to the high rates of obesity, diabetes, metabolic syndrome in this group.[25,46,48]

Acknowledgments

Financial support for this study was provided by the Instituto Mexicano del Seguro Social (IMSS) and the Consejo Nacional de Ciencia y Tecnología (CONACYT) grants #26267M and SALUD-2011-01-161930. Ms. Auslander received grants from the Blum Center and the Dean's Global Health Fellowship at UCLA to support her work on this study. Dr. Crespi was supported by NIH UL1TR000124. The authors are very grateful to the Health Worker Cohort Study participants and their families, as well as the nurses and staff at IMSS. We also thank Paula Ramírez for providing statistical support.

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J Dig Dis. Author manuscript; available in PMC 2017 May 01.

Table 1

Characteristics of study sample and participants with elevated ALT[a] levels at Wave 1 and Wave 2. (N= 1,462)

	Wave 1				Wave 2			
	Total (N, %)	**Elevated n= 245**	**Proportion Elevated**	**P- Value[b]**	**Total (N, %)**	**Elevated n= 212**	**Proportion Elevated**	**P- Value[b]**
Sex								
Female	1099 (75)	140	0.13		1099 (75)	137	0.12	
Male	363 (25)	105	0.29	0.00	363 (25)	75	0.21	0.00
Age								
≤ 39	488 (33)	82	0.17		224 (15)	40	0.18	
40–59	749 (51)	139	0.19		801 (55)	137	0.17	
≥ 60	225 (15)	24	0.11	0.02	437 (30)	35	0.08	0.00
Education Status								
Less than High School	445 (30)	77	0.17		438 (30)	57	0.13	
High School graduate	273 (19)	50	0.18		270 (19)	44	0.16	
More than High School	744 (51)	118	0.16	0.61	754 (52)	111	0.15	0.47
BMI[c]								
Normal	570 (39)	40	0.07		501 (34)	33	0.07	
Overweight	618 (42)	114	0.18		652 (45)	104	0.16	
Obese	274 (19)	91	0.33	0.00	309 (21)	75	0.24	0.00
Diabetes[d]								
No	1358 (93)	213	0.16		1264 (86)	168	0.13	
Yes	104 (7)	32	0.31	0.00	198 (14)	44	0.22	0.00
Metabolic Syndrome[e]								
No	1044 (72)	136	0.13		837 (57)	96	0.11	
Yes	418 (28)	109	0.26	0.00	625 (43)	116	0.19	0.00
Alcohol[f]								
Nondrinker/Moderate	1208 (83)	173	0.14		975 (88)	117	0.12	

	Wave 1				Wave 2			
	Total (N, %)	**Elevated n= 245**	**Proportion Elevated**	**P- Value[b]**	**Total (N, %)**	**Elevated n= 212**	**Proportion Elevated**	**P- Value[b]**
Heavy/Binge	254 (17)	72	0.28	0.00	137 (12)	24	0.18	0.07

[a] Elevated alanine aminotransferase (ALT) was defined as ALT > 40 IU/L for males and females.

[b] P-value was computed using the Chi-squared test.

[c] Body mass index (BMI) was defined as normal <25 kg/m^2, overweight between 25–30 kg/m^2, or obese ≥ 30 kg/m^2.

[d] Diabetes status was determined based on participant's medical history, current use of diabetes medications, and/or a plasma glucose level > 125 mg/dL.

[e] We defined Metabolic Syndrome according to the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III).

[f] Alcohol intake was defined as follows: nondrinkers- no history of drinking, moderate- 1 drink a day for females and 1–2 drinks per day for males, heavy- 2–4 drinks per day for females and 3–4 for males, binge- 5 or more drinks per day for both females and males.

Table 2

Cross-sectional analysis of risk factors for elevated ALT[a] levels in Wave 1 (2004 – 2007) and Wave 2 (2011 – 2013). (N= 1,462)

	Wave 1			Wave 2		
	Model 1[b]	Model 2[b]	Model 3[b]	Model 1[b]	Model 2[b]	Model 3[b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sex						
Female	1.00	1.00	1.00	1.00	1.00	1.00
Male	2.8 (2.1 – 3.7)**	2.6(1.9 – 3.5)**	2.3 (1.7 – 3.2)**	1.8 (1.3 – 2.5)**	1.7 (1.2 – 2.3)**	1.7 (1.2 – 2.4)**
Age						
≤ 39	1.7 (1.0 – 2.7)*	2.1(1.3 – 3.5)**	2.1 (1.3 –3.8)**	2.5 (1.5 – 4.1)**	2.8 (1.7 – 4.6)**	2.7 (1.6 – 4.7)**
40–59	1.9 (1.2 – 3.0)**	2.0 (1.2 – 3.2)**	2.0 (1.2 – 3.4)**	2.4 (1.6 – 3.5)**	2.4 (1.6 – 3.6)**	2.4 (1.5 – 3.6)**
≥ 60	1.00	1.00	1.00	1.00	1.00	1.00
BMI[e]						
Normal	1.00	1.00	1.00	1.00	1.00	1.00
Overweight	3.0 (2.0 – 4.4)**	2.9 (2.0 – 4.3)**	2.9 (2.0 – 4.3)**	2.7 (1.8 – 4.1)**	2.8 (1.8 – 4.2)**	2.8 (1.8 – 4.2)**
Obese	6.6 (4.3 – 9.9)**	6.9 (4.5 – 10.4)**	6.6 (4.3 – 10.1)*	4.5 (2.9 – 7.0)**	4.8 (3.0 – 7.4)**	4.7 (3.0 – 7.4)**
Diabetes[f]						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	2.4 (1.5 – 3.7)**	2.1 (1.3 – 3.5)**	2.1 (1.3 – 3.5)**	1.9 (1.3 – 2.7)**	1.9 (1.3 – 2.8)**	1.9 (1.3 – 2.9)**
Metabolic Syndrome[g]						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	2.4 (1.8 – 3.1)**	1.7 (1.2 – 2.3)**	1.7 (1.2 – 2.3)**	1.8 (1.3 – 2.4)**	1.3 (1.0 – 1.9)	1.3 (1.0 – 1.9)
Alcohol[h]						
Nondrinker/Moderate	1.00	1.00	1.00	1.00	1.00	1.00
Heavy/Binge	2.4 (1.7 – 3.2)**	1.4 (1.0 – 2.1)*	1.5 (1.0 – 2.1)*	1.6 (1.0 – 2.5)	1.1 (0.7 –1.9)	1.2 (0.7 – 2.0)

[a] Elevated alanine aminotransferase (ALT) was defined as ALT > 40 IU/L for males and females.

[b] Model 1: Unadjusted

[c] Model 2: Adjusted for age, sex, BMI

[d] Model 3: Adjusted for age, sex, BMI, alcohol, education

[e] Body mass index (BMI) was defined as normal <25 kg/m^2, overweight between 25–30 kg/m^2, or obese ≥30 kg/m^2.

[f] Diabetes status was determined based on participant's medical history, current use of diabetes medications, and/or a plasma glucose level > 125 mg/dL.

[g] We defined Metabolic Syndrome according to the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III).

[h] Alcohol intake was defined as follows: nondrinkers- no history of drinking, moderate- 1 drink a day for females and 1–2 drinks per day for males, heavy- 2–4 drinks per day for females and 3–4 for males, binge- 5 or more drinks per day for both females and males. Participants missing alcohol data in Wave 2 (n= 347).

[*] P < 0.01 for test of null hypothesis that the odds ratio is equal to the odds ratio in the reference category.

[**] P < 0.05 for test of null hypothesis that the odds ratio is equal to the odds ratio in the reference category.

Table 3

Association between change in risk factor status from Wave 1 (W1) to Wave 2 (W2) and risk of elevated ALT[a] among participants who had normal ALT levels at Wave 1. (N= 1,217)

	Model 1[b]	Model 2[c]	Model 3[d]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sex			
Female (n= 959)	1.00	1.00	1.00
Male (n= 258)	1.1 (0.7 – 1.8)	1.2 (0.7 – 1.9)	1.3 (0.8 – 2.2)
Age			
≤ 39 (n = 406)	3.7 (1.5 – 8.8) **	3.7 (1.5 – 9.0) **	4.2 (1.6 – 10.8) **
40–59 (n = 610)	3.7 (1.6 – 8.8) **	3.6 (1.5 –8.5) **	3.8 (1.6 – 9.3) **
≥ 60 (n= 201)	1.00	1.00	1.00
BMI[e] (from W1 – W2)			
Remained Normal (n= 390)	1.00	1.00	1.00
Weight Loss[f] (n= 92)	1.5 (0.6 – 4.0)	1.6 (0.6 – 4.3)	1.6 (0.6 – 4.3)
Remained Overweight (n= 379)	2.4 (1.3 – 4.3) **	2.5 (1.4 – 4.6) **	2.5 (1.4 – 4.6) **
Remained Obese (n= 150)	2.8 (1.4 – 5.7) **	3.0 (1.5 – 6.2) **	3.1 (1.5 – 6.3) **
Weight Gain[g] (n= 201)	4.2(2.2 – 7.7) **	4.0 (2.2 – 7.5) **	4.1 (2.2 – 7.6) *
Diabetes[h] (from W1 – W2)			
Never Diabetic (n= 1,081)	1.00	1.00	1.00
Remained Diabetic (n= 72)	1.2 (0.5 – 2.6)	1.7 (0.7 – 4.0)	1.7 (0.7 – 4.0)
Developed Diabetes (n= 64)	2.5 (1.3 – 4.9) **	2.7 (1.3 – 5.4) **	2.7 (1.3 – 5.4) **
Metabolic Syndrome[i] (MS) (from W1 – W2)			
Never had MS (n= 648)	1.00	1.00	1.00
Remained with MS (n= 228)	1.8 (1.0 – 3.0) *	1.8 (1.0 – 3.4)	1.8 (1.0 – 3.4)
Developed MS (n= 260)	2.7 (1.7 – 4.3) **	2.3 (1.4 – 3.8) **	2.2 (1.3 – 3.7) **
No Longer have MS (n= 81)	2.2 (1.1 – 4.6) *	2.3 (1.1 – 5.0) *	2.2 (1.0 – 4.9) *

[a] Elevated alanine aminotransferase (ALT) was defined as ALT > 40 IU/L for males and females.

[b] Model 1: Unadjusted

[c] Model 2: Adjusted for age, sex, BMI

[d] Model 3: Adjusted for age, sex, BMI, alcohol, education

[e] Body mass index (BMI) was defined as normal <25 kg/m^2, overweight between 25–30 kg/m^2, and obese ≥ 30 kg/m^2.

[f] Weight loss was defined as any of the following changes in BMI status from W1 to W2: obese (W1) – overweight (W2), obese (W1) – normal (W2), or overweight (W1) – normal (W2)

[g] Weight gain was defined as any of the following changes in BMI status from W1 to W2: normal (W1) – overweight (W2), normal (W1) – obese (W2), overweight (W1) – obese (W2)

[h] Diabetes status was determined based on participant's medical history, current use of diabetes medications, and/or a plasma glucose level > 125 mg/dL.

[i] We defined Metabolic Syndrome according to the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III).

[*] $P < 0.01$ for test of null hypothesis that the odds ratio is equal to the odds ratio in the reference category.

[**] $P < 0.05$ for test of null hypothesis that the odds ratio is equal to the odds ratio in the reference category.