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Elevated Serum Liver Enzymes and Fatty Liver Changes Associated With Long Driving Among Taxi Drivers

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Background *Previous studies suggested increased morbidities and mortalities of liver diseases in drivers.*

Methods *To examine whether driving (monthly driving distance; tenure) is associated with elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), or chronic fatty liver (FL) changes, we performed a cross-sectional, secondary analysis of the Taxi Drivers' Health Study (n = 1,355), adjusting for clinical, demographic, and lifestyle factors.*

Results *Prevalence of elevated ALT, elevated AST, and fatty liver changes were 22.0%, 5.1%, and 9.3%, respectively. Driving distance had a positive association with elevated ALT with a prevalence ratio of 1.35 (95% CI: 0.98, 1.89) comparing the highest versus lowest driving quartile. This association differed by alcohol use, with a corresponding prevalence ratio of 2.08 (95% CI: 1.30, 3.33) among "past/current" drinkers but no association among "never" drinkers. Similar patterns were found for AST, but estimates were less stable. We found a curvilinear response pattern for fatty liver changes; prevalence first increased with years as a taxi driver and then receded in the highest ranges of driving tenure, regardless of the alcohol history.*

Conclusions *Our results provide evidence that long driving is associated with both short-term and chronic liver insults, although alcohol use appears to modify this putative effect.* Am. J. Ind. Med. 54:618–627, 2011. *© 2011 Wiley-Liss, Inc.*

KEY WORDS: fatty liver disease; professional driving; occupational epidemiology; taxi drivers; alanine aminotransferase

INTRODUCTION

Fatty liver disease represents a spectrum of liver disorders ranging from mild steatosis to steatohepatitis and can progress to more severe forms such as fibrosis and cirrhosis and rarely to hepatocellular carcinoma [Clark, 2006]. Alcohol abuse is a well-established cause of fatty liver disease. However, alcohol abuse is not a necessary cause of fatty liver disease. In the early 1980s, non-alcoholic fatty liver disease (NAFLD) was first recognized as a disease entity. NAFLD now affects a large and increasing proportion of the global population, with prevalence estimates in both the U.S. and the Asia-Pacific region ranging from 5% to 30% [Clark, 2006; Chitturi et al., 2007]. Prevalence estimates for Taipei City, Taiwan, the study site, are not available, but a study in a rural village

Additional Supporting Information may be found in the online version of this article.

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of Taiwan estimated the prevalence of NAFLD to be 11.5% [Chen et al., 2006]. Obesity and type 2 diabetes mellitus are known to be associated with NAFLD and the disease is widely considered the ''hepatic manifestation of the metabolic syndrome'' [Cave et al., 2007]. Moreover, several recent studies suggest that NALFD increases the risk of all-cause mortality, cardiovascular disease mortality, and liver disease mortality [Dunn et al., 2008; Ong et al., 2008].

Though diet and lifestyle factors may be the primary culprits in fatty liver disease, occupational and environmental exposures may also contribute. A prior study of municipal police officers exposed to urban air pollution found increased serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, markers of recent liver damage, when compared to office workers [Tomao et al., 2002]. Another study, which compared gas station attendants, taxi drivers, and bus drivers to a set of controls, found that both gas station attendants and taxi drivers had significantly higher AST than the control group, though only gas station attendants had elevated levels of ALT [Kapaki et al., 1998]. An occupational health surveillance study in Canada found that lorry drivers had an increased risk of mortality due to non-alcoholic cirrhosis [Aronson et al., 1999]. Other studies have found increased risk of cirrhosis in professional drivers and other workers exposed to diesel exhaust, though the authors of one of those studies [Gubéran et al., 1992] suggest that the increase was attributable to alcohol abuse [Boffetta et al., 1988; Gubéran et al., 1992].

In the current analysis we examine the association between average monthly driving, and tenure as a professional taxi driver, and three outcome measures: elevated serum ALT and AST levels, which reflect recent liver insults, and fatty liver changes, diagnosed by abdominal ultrasonography, which reflect chronic liver damages. We hypothesize that the long driving is associated with both short- and long-term liver injuries.

MATERIALS AND METHODS

We conducted a secondary data analysis using data from the Taxi Drivers' Health Study (TDHS). The TDHS was conducted as part of a medical monitoring program that offered free medical examinations to taxi drivers in Taipei City, Taiwan in 2000. Details on the study, including results showing that enrolled drivers were demographically similar to unenrolled drivers and to reference statistics for all taxi drivers in Taipei City have been described elsewhere [Chen et al., 2004a,b]. Briefly, the Taipei City Government selected five hospitals as the provider of the medical monitoring. Between January 31 and May 31, 3,295 taxi drivers participated in this program and those who were examined in the hospital with the largest service volume became the study base of the THDS ($n = 1,355$). Drivers were eligible for TDHS enrollment if they were registered taxi drivers in Taipei City for at least 1 year and were able to read.

The research protocols and consent forms were approved by the institutional review board of the Taipei Veterans General Hospital, Taipei, Taiwan. Informed consent was obtained from every TDHS participant in the selected hospital. The secondary data analysis presented here was approved by the institutional review board of the University of North Carolina, Chapel Hill.

Outcome Measures

Fasting blood samples were drawn and analyzed for clinical biochemistry including ALT and AST using the Hitachi autoanalyzer model 7150 (Hitachi Corp, Tokyo, Japan). Our primary analyses focus on elevation of ALT (>40 IU/L) to reflect short-term abnormalities, because ALT is a more sensitive and specific indicator of liver injury as compared to AST. While both ALT and AST are present in the liver, AST is also present in many other organs and thus elevations of AST may reflect damage to organs other than the liver [Pratt and Kaplan, 2000]. Similar approaches of using ALT elevation to define liver damages have been used in other population-based studies [Ruhl and Everhart, 2003; Ioannou et al., 2006; Chen et al., 2007; Dunn et al., 2008]. Supplementary analyses examined prevalence of elevated AST (>40 IU/L). Serum samples were also tested for hepatitis B surface antigen (HBsAg) by ELISA (Auszyme Monoclonal, Abbott Park, IL) and for antihepatitis C virus antibody (anti-HCV) by the third-generation enzyme immunoassay (EIA.3.0, Abbott Laboratories, Chicago, IL).

Abdominal ultrasonography (Toshiba Tosbee, Tokyo, Japan, model SSA-340 equipped with a 3.75 MHz convex-type transducer) was performed by board-certified specialists in gastroenterology and hepatology or trained radiologists blind to the occupational characteristics and driving histories of study subjects. Following the published guideline [Saverymuttu et al., 1986], the examiners determined the presence of fatty liver on the basis of diffusely increased liver echogenicity with evident contrast between the liver and the kidney, diffusely increased liver echogenicity with blurring of the intrahepatic vessels and the diaphragm, or bright hepatic echogenicity with poor penetration of the posterior hepatic segments and poor or no visualization of intrahepatic vessels and diaphragm. According to published scoring systems [Yajima et al., 1983; Tam and Wu, 1986], examiners also rated the degrees of increased echogenicity (including brightness compared to kidneys, blurring of gall bladder wall, blurring of

hepatic veins, blurring of portal vein, and far gain attenuation) and gave an overall assessment (mild, moderate, or severe) on severity. In the present study, subjects with moderate or severe increases in liver echogenecity were classified as having significant fatty liver changes. We defined suspected NAFLD cases based on empirical data, including (1) having ultrasonographic evidence of fatty liver, (2) being negative for hepatitis B and C, and (3) self-identification as a ''never'' drinker of alcohol.

Measurement of Exposure and Covariates

A standardized, self-administered questionnaire was used to collect information on taxi driving exposure as well as other demographic and lifestyle covariates. Taxi driving exposure was quantified as monthly driving distance (kilometers) and years of professional tenure as a taxi driver. Self-report of driving distance was validated in an exposure assessment substudy [Chen et al., 2004c]. Furthermore, taxi drivers in Taipei City commonly track their mileage on a daily basis, either to estimate their individual income or for reporting to supervisors at their taxicab company.

Drivers were categorized as either ''never drinkers,'' ''past drinkers,'' or ''current drinkers'' based on self-reported alcohol use. Detailed data on the frequency and quantity of alcohol consumption were not assessed, nor was the period since alcohol use cessation recorded for those who identified as ''past'' drinkers. In the absence of these detailed alcohol use distinctions, past and current drinkers were combined in a single ''drinker'' category. Smoking was similarly grouped (never, past, or current smokers). Frequency of exercise was classified as ''seldom/never,'' ''0–1 times per week,'' or ''more than 1 time per week.'' Age was collected as a continuous variable and categorized in three groups ($<$40, 40–49, and $\geq$50 years).

Additional covariate data were drawn from medical examination records and laboratory results. Height and weight were used to calculate body mass index (BMI), which was categorized into ''normal'' ($<$24 kg/m^2), ''overweight'' (24–27 kg/m^2), or ''obese'' ($\geq$27 kg/m^2), based on BMI guidelines for the Taiwanese population [Department of Health, 2004]. Standard clinical cut-points were used to classify drivers as having diabetes (fasting sugar $>$126 mg/dl), hypertension (measured systolic/diastolic blood pressures $>$140/90 mmHg), high triglycerides ($\geq$160 mg/dl), or abnormal total cholesterol (''borderline high'' 200–239 mg/dl, or ''high'' $>$240 mg/dl total cholesterol) [Chen et al., 2005]. Drivers could also be classified as diabetic or hypertensive if they had physician diagnoses for those conditions with subsequent treatment.

Exclusions and Missing Data

From the total study group of 1,355, 1,242 (92%) completed the self-administered questionnaire. Two hundred eighteen participants were excluded from the analysis because they tested positive for HBsAg (197), hepatitis C antibody (16), or both (5). Of the 1,024 remaining participants, 44 did not provide monthly driving data and 10 did not provide professional driving tenure information, so the final effective *maximum* sample size was 980 for analyses where monthly driving distance was the main exposure and 1,014 for analyses of long-term driving exposure.

Statistical Analysis

Separate analyses were performed for the two outcome measures studied. Potential covariates to include in regression models were identified through assessment of a directed acyclic graph, a causal diagram that is used in epidemiologic research to describe the assumed causal relationships between exposure, covariate, and outcome variables [Greenland et al., 1999; Rothman et al., 2008]. Our primary analyses were conducted examining the total association between long driving and the two study outcomes. Given our interest in the potential role of exposures other than diet and exercise, we also conducted analyses conditioning on additional measured covariates related to those metabolic factors (BMI, exercise frequency, hypertension, and diabetes) in order to control for any indirect effects of driving on fatty liver disease operating through those paths [Cole and Hernan, 2002].

Binary indicator (dummy) variable coding was used for all categorical and ordinal variables. Multiple log-binomial regression was used to estimate prevalence ratios contrasting each quartile of driving exposure to the lowest quartile [Deddens and Petersen, 2008]. Covariates that appeared to be strong effect measure modifiers in the tabular analysis were included as product terms with the main exposure in the regression models. Since ultrasonographic imaging is not able to distinguish between alcohol-related and non-alcoholic fatty liver diseases, statistical analyses were stratified by alcohol use history. Effect measure modification was assessed using a likelihood ratio test of the product term with an a priori criterion of $P < 0.15$. All statistical analyses were performed using Stata statistical software version 9.2 (StatCorp LP, College Station, TX).

RESULTS

Reported monthly driving distances in kilometers per month (km/mo.) ranged from 500 to 8,700 km per month, with a mean of 4,399 km/mo. and median of 4,480 km/mo. Monthly driving distance was categorized into

quartiles, resulting in the following groupings: 500 to <3,380, ≥3,380 to <4,480, ≥4,480 to <5,400, and ≥5,400 km/mo. Mean years working as a professional taxi driver was 11.5 (SD 7.9), with a range of 1–40 years. Occupational tenure was divided into quartiles with groupings at 1 to <5, 5 to <10, 10 to <16, and 16 or more years of professional taxi driving. Table I describes the distribution of other demographic, occupational, and clinical characteristics of the study population.

Elevated ALT and AST Results

Prevalence results and crude and age–sex-adjusted prevalence ratios for elevated ALT, elevated AST, and fatty liver changes are summarized in Tables II–IV, respectively. Of the 1,022 drivers who completed the questionnaire and were not excluded due to positive tests results for hepatitis B or C, 225 (22%) had elevated serum ALT (>40 IU/L). Overall, the prevalence of elevated ALT

TABLE I. Demographic, Occupational, and Clinical Characteristics of the 1,024* Participants in the Taxi Drivers' Health Study (TDHS), Stratified by Self-Reported Alcohol Use

	Monthly driving distance (km/mo.)				Years of taxi driving			
	Never drinkers		Past/current drinkers		Never drinkers		Past/current drinkers	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Sex								
Male	438	4457.8 (1492.7)	498	4419.8 (1499.3)	449	11.52 (7.83)	521	11.48 (7.80)
Female	29	3616.6 (1406.2)	13	3155.4 (1328.9)	32	11.78 (8.51)	12	15.58 (10.52)
Age								
<40 years	143	4556.5 (1576.3)	143	4468.8 (1642.0)	149	7.20 (3.78)	155	6.47 (3.28)
40–49 years	186	4587.6 (1392.8)	234	4542.5 (1440.2)	190	11.38 (6.46)	241	11.70 (6.75)
≥50 years	138	4004.0 (1492.0)	134	4030.6 (1421.7)	142	16.31 (9.83)	137	17.12 (9.47)
BMI (kg/m^2)								
<24	203	4487.8 (1469.5)	200	4241.2 (1446.0)	210	11.17 (7.92)	204	11.15 (7.84)
24–27	155	4332.6 (1456.3)	187	4342.5 (1526.0)	156	11.39 (7.83)	197	11.41 (7.69)
>27	109	4356.5 (1619.0)	124	4691.8 (1544.0)	115	12.42 (7.81)	132	12.48 (8.21)
Diabetes status								
Not diabetic	409	4362.8 (1514.6)	457	4372.0 (1510.1)	422	11.25 (7.64)	474	11.32 (7.59)
Diabetic (fasting blood sugar >126 mg/dl or physician diagnosed diabetes with subsequent treatment)	58	4707.1 (1366.3)	54	4520.2 (1489.9)	59	13.66 (9.13)	59	13.61 (9.78)
Hypertension								
<140/90 mmHg	413	4427.8 (1504.1)	414	4401.4 (1523.4)	426	11.02 (7.54)	433	11.02 (7.57)
≥140/90 mmHg or physician diagnosed hypertension with subsequent treatment	54	4235.8 (1470.0)	97	4328.8 (1442.3)	55	15.62 (9.09)	100	13.95 (8.76)
Total cholesterol								
Normal (<200 mg/dl)	148	4455.1 (1414.7)	149	4338.7 (1501.7)	152	10.80 (6.80)	155	10.25 (8.14)
Borderline high (200–239 mg/dl)	178	4304.2 (1563.1)	202	4330.3 (1544.5)	185	10.97 (7.45)	206	12.23 (7.95)
High (≥240 mg/dl)	141	4481.6 (1508.7)	160	4505.6 (1466.8)	144	13.06 (9.16)	172	11.97 (7.45)
Triglycerides								
<160 mg/dl	309	4340.9 (1523.1)	335	4319.8 (1510.6)	318	11.89 (7.95)	346	11.32 (7.76)
≥160 mg/dl	158	4532.2 (1449.9)	176	4516.7 (1496.6)	163	10.87 (7.67)	187	12.05 (8.10)
Smoking								
Never smoker	250	4236.7 (1506.6)	188	4321.2 (1531.3)	251	12.62 (8.36)	195	12.47 (8.57)
Past smoker	54	4775.3 (1472.1)	67	4297.0 (1411.7)	58	9.32 (6.16)	68	11.45 (7.77)
Current smoker	155	4497.4 (1464.7)	237	4453.3 (1541.1)	163	10.70 (7.38)	250	10.65 (7.29)
Exercise								
Seldom/never	259	4405.8 (1526.6)	279	4438.9 (1557.6)	267	11.30 (7.60)	290	11.64 (7.85)
0–1 times per week	95	4529.7 (1449.5)	112	4470.4 (1440.9)	100	10.29 (7.13)	118	10.83 (7.36)
More than 1 time per week	112	4285.8 (1482.7)	120	4191.1 (1442.2)	113	13.19 (8.85)	125	12.12 (8.43)

*After exclusion of 218 drivers who tested positive for hepatitis B surface antigen or hepatitis C antibody.

TABLE II. Summarized Results of Prevalence and Crude and Adjusted Prevalence Ratios From Log-Binomial Regression Models Estimating the Association Between Monthly Driving Distance and Elevated Alanine Aminotransferase (ALT >40 IU/L) Among 1,024* Taxi Drivers in the Taxi Drivers Health Study, Taiwan, 2000

	Prevalence (%)			Crude prevalence ratios (95% CIs)			Adjusted[a] prevalence ratios (95% CIs)		
Monthly driving distance (km)	Overall (n = 980[b])	Never drinkers (n = 467)	Past and current drinkers (n = 511)	Overall	Never drinkers	Past and current drinkers	Overall	Never drinkers	Past and current drinkers
1st quartile (500 to <3,380)	18.3	21.6	15.2	1.00	1.00	1.00	1.00	1.00	1.00
2nd quartile (≥3,380 to <4,480)	17.3	19.4	15.8	0.95 (0.65, 1.39)	0.90 (0.54, 1.51)	1.04 (0.59, 1.83)	0.92 (0.63, 1.35)	0.86 (0.52, 1.43)	1.03 (0.59, 1.81)
3rd quartile (≥4,480 to <5,400)	23.3	22.2	24.5	1.28 (0.89, 1.83)	1.03 (0.63, 1.68)	1.61 (0.94, 2.76)	1.17 (0.82, 1.68)	0.93 (0.58, 1.51)	1.50 (0.88, 2.55)
4th quartile (≥5,400 to 8,700)	27.2	19.0	34.5	1.49 (1.07, 2.07)	0.88 (0.54, 1.46)	2.27 (1.42, 3.63)	1.35 (0.98, 1.89)	0.80 (0.48, 1.31)	2.08 (1.30, 3.33)

*After exclusion of 218 drivers who tested positive for hepatitis B surface antigen or hepatitis C antibody.
[a]Adjusted for: age, sex.
[b]Forty-four drivers did not provide monthly driving distance information; number of never drinkers and past/current drinkers does not sum to 980 because 2 drivers were missing alcohol use history.

TABLE III. Summarized Results of Prevalence and Crude and Adjusted Prevalence Ratios From Log-Binomial Regression Models Estimating the Association Between Monthly Driving Distance and Elevated Aspartate Aminotransferase (AST >40 IU/L) Among 1,024* Taxi Drivers in the Taxi Drivers Health Study, Taiwan, 2000

	Prevalence (%)			Crude prevalence ratios (95% CIs)			Adjusted[a] prevalence ratios (95% CIs)		
Monthly driving distance (km)	Overall (n = 980[b])	Never drinkers (n = 467)	Past and current drinkers (n = 511)	Overall	Never drinkers	Past and current drinkers	Overall	Never drinkers	Past and current drinkers
1st quartile (500 to <3,380)	3.3	4.3	2.4	1.00	1.00	1.00	1.00	1.00	1.00
2nd quartile (≥3,380 to <4,480)	2.8	0.9	4.3	0.85 (0.31, 2.31)	0.21 (0.03, 1.81)	1.80 (0.46, 7.04)	0.83 (0.31, 2.27)	0.21 (0.03, 1.78)	1.77 (0.45, 6.95)
3rd quartile (≥4,480 to <5,400)	8.2	6.8	9.8	2.48 (1.10, 5.58)	1.59 (0.53, 4.71)	4.08 (1.15, 14.45)	2.36 (1.04, 5.34)	1.52 (0.51, 4.55)	3.94 (1.11, 14.03)
4th quartile (≥5,400 to 8,700)	6.3	2.4	9.7	1.88 (0.83, 4.28)	0.55 (0.14, 2.26)	4.02 (1.18, 13.68)	1.79 (0.78, 4.10)	0.53 (0.13, 2.19)	3.86 (1.13, 13.23)

*After exclusion of 218 drivers who tested positive for hepatitis B surface antigen or hepatitis C antibody.
[a]Adjusted for: age, sex.
[b]Forty-four drivers did not provide monthly driving distance information; number of never drinkers and past/current drinkers does not sum to 980 because 2 drivers were missing alcohol use history.

TABLE IV. Summarized Results of Prevalence and Crude and Adjusted Prevalence Ratios From Log-Binomial Regression Models Estimating the Association Between Years of Professional Taxi Driving and Ultrasonographically Detected Fatty Liver Disease Among 1,024* Taxi Drivers in the Taxi Drivers Health Study, Taiwan, 2000

Professional taxi driving tenure (years)	Prevalence (%)			Crude prevalence ratios (95% CIs)			Adjusted[a] prevalence ratios (95% CIs)		
	Overall (n = 1,014[b])	Never drinkers (n = 481)	Past and current drinkers (n = 533)	Overall	Never drinkers	Past and current drinkers	Overall	Never drinkers	Past and current drinkers
1st quartile (<5)	5.0	5.7	4.5	1.00	1.00	1.00	1.00	1.00	1.00
2nd quartile (≥5 to <10)	10.6	9.0	12.4	2.12 (1.06, 4.24)	1.59 (0.58, 4.30)	2.78 (1.06, 7.30)	2.12 (1.06, 4.24)	1.66 (0.61, 4.50)	2.69 (1.02, 7.06)
3rd quartile (≥10 to <16)	11.5	12.6	10.4	2.29 (1.15, 4.57)	2.22 (0.84, 5.83)	2.32 (0.86, 6.25)	2.17 (1.08, 4.36)	2.22 (0.84, 5.83)	2.10 (0.77, 5.70)
4th quartile (≥16)	8.9	10.8	7.4	1.78 (0.87, 3.65)	1.91 (0.71, 5.15)	1.65 (0.59, 4.62)	1.56 (0.74, 3.29)	1.70 (0.62, 4.67)	1.42 (0.49, 4.07)

* After exclusion of 218 drivers who tested positive for hepatitis B surface antigen or hepatitis C antibody.
[a] Adjusted for: age, sex.
[b] Ten drivers did not provide data on professional driving tenure.

increased as monthly driving distance increased (Table II), though this increase was not strictly monotonic. The prevalence among drivers in the highest quartile of monthly driving distances was 1.49 (95% CI: 1.07, 2.07) times that among the group with the lowest monthly driving distances. After adjusting for age and sex, this contrast yielded a prevalence ratio of 1.35 (95% CI: 0.98, 1.89). In a trend test using integer scoring for the quartiles, the prevalence ratio for each quartile increment was 1.13 (95% CI: 1.02, 1.26; *P*-value for trend test: 0.023).

When the analysis was stratified by history of alcohol use, distinct patterns emerged for never drinkers and past/current drinkers. Among never drinkers, there appeared to be no association between monthly driving distance and prevalence of elevated ALT (Table II). Instead, the incremental trend observed in the non-stratified results appeared to derive primarily from the group who identified themselves as being past or current drinkers. Among those who reported past or current alcohol use, each increasing quartile of monthly driving was associated with an increase in the prevalence of elevated ALT. In the group of alcohol users, the prevalence ratio comparing individuals in highest quartile of monthly driving to those driving the least was 2.27 (95% CI: 1.42, 3.63). Adjustment for age and sex in the binomial regression analyses attenuated the strength of this association, but did not appreciably alter the trends observed in the crude analyses. Further adjustment by BMI, exercise frequency, diabetes, and hypertension to separate out the indirect effects of long driving operating through the alternate pathway involving metabolic factors changed the estimates moderately, but did not substantively change the observed patterns (Table V).

Supplementary analyses examining elevations in AST showed similar patterns of association to those obtained using elevated ALT as the outcome, though overall prevalence of elevated AST (5.1%) was much lower and the estimates of associations were unstable (Table III), largely due to the small number of cases with elevated AST in the reference category (N = 3 for the 2.4% in 1st quartile of driving among past/current drinkers) in stratified analyses.

Ultrasonically Detected Fatty Liver Disease Results

Evidence of fatty liver disease was detected by abdominal ultrasonographic examination in 94 (9.3%) of the 1,014 drivers who reported their professional taxi driving tenure in years, were not excluded due to infectious hepatitis, and had complete medical examinations. Evidence of fatty liver disease was most prevalent in drivers with 10–16 years of professional taxi driving (3rd quartile) and least prevalent in those with under 5 years (1st quartile) (Table IV). In a post hoc contrast

TABLE V. Adjusted Prevalence Ratios From Log-Binomial Regression Models Estimating the Association Between (a) Monthly Driving Distance and Elevated Serum Alanine Aminotransferase and (b) Years of Professional Taxi Driving and Ultrasonographically Detected Fatty Liver Disease Among 1,024* Taxi Drivers in the Taxi Drivers Health Study, Taiwan, 2000

	Adjusted prevalence ratios (95% CIs)[a]	
	Never drinkers	Past and current drinkers
Monthly driving distance (km)[b]		
1st quartile (500 to <3,380)	1.00	1.00
2nd quartile (≥3,380 to <4,480)	0.88 (0.56, 1.40)	0.99 (0.58, 1.70)
3rd quartile (≥4,480 to <5,400)	1.02 (0.66, 1.57)	1.54 (0.92, 2.56)
4th quartile (≥5,400 to 8,700)	0.85 (0.54, 1.35)	1.73 (1.10, 2.73)
Professional taxi driving tenure (years)[b]		
1st quartile (<5)	1.00	1.00
2nd quartile (≥5 to <10)	1.40 (0.55, 3.52)	2.82 (1.13, 7.06)
3rd quartile (≥10 to <16)	1.69 (0.68, 4.18)	2.10 (0.83, 5.33)
4th quartile (≥16)	1.13 (0.43, 2.96)	1.34 (0.50, 3.61)

*After exclusion of 218 drivers who tested positive for hepatitis B surface antigen or hepatitis C antibody.
[a]Adjusted for: age, sex, body mass index, hypertension, diabetes, exercise.
[b]Forty-seven and 13 drivers were missing data on one or more variables in the driving distance and tenure analyses, respectively.

comparing individuals driving 5 or more years to those with <5 years of driving exposure, the prevalence ratio, adjusted for age and sex, was 1.99 (95% CI: 1.04, 3.79). Overall, and within both strata of alcohol use history, the prevalence first increased with driving tenure then lowered slightly at the highest ranges of years driving. These nonlinear patterns of association between professional tenure and evidence of fatty liver disease persist after adjusting for the effects of age and sex. The peak prevalence occurred in the 3rd quartile among never drinkers, but in the 2nd quartile among past and current drinkers, which suggests that development of fatty liver damage as a result of occupational exposure may occur more rapidly among those who consume alcohol. After additional adjustment for indirect effects operating through the pathway involving BMI, exercise, diabetes, and hypertension (Table V), the results were slightly attenuated, but retained the exposure–response pattern observed in the crude and age–sex-adjusted results.

DISCUSSION

This study provides evidence that increases in monthly driving distance and tenure as a professional taxi driver, respectively, increase the prevalence of elevated ALT, elevated AST, and ultrasonographically detectable fatty liver changes. Furthermore, the results of the stratified analyses suggest that current or previous alcohol use may strengthen the associations between long driving and putative liver damages. Our study results are consistent with prior studies relating liver injury and professional driving and similar occupations [Gubéran et al., 1992; Kapaki et al., 1998; Aronson et al., 1999; Tomao et al., 2002], though none of these studies (including this one) provide direct information regarding the specific occupational exposure(s) that may be acting in this relationship.

We speculate that urban air pollution may be one plausible agent to consider in future studies for the following reasons. First, previous studies on taxi drivers and other vehicle-based professionals in urban settings have reported high in-vehicle exposure levels [Zagury et al., 2000; Jo and Yu, 2001; Riediker et al., 2003]. Second, air pollution and its components have previously been considered as potential hepatotoxins [Winkelstein and Gay, 1971; Morris and Shapiro, 1972; Folkmann et al., 2007; Tomaru et al., 2007]. Third, recent toxicological studies show elevated ALT levels in response to exposure to diesel exhaust particles (DEP) [Tomaru et al., 2007], and accumulative data from studies on DEP toxicity in animals have pointed to increased hepatic oxidative stress [Folkmann et al., 2007]. Traffic remains the primary source of particular air pollution in Taipei City. Although Taipei City is not the most polluted area in Taiwan and its air quality has significantly improved, the concentration of fine particles (with aerodynamic diameter $<2.5\ \mu m$) monitored at a supersite in 2002–2008 was approximately two times of current air quality standard ($15\ \mu g/m^3$) for annual average in the US [Chang et al., 2010]. The automobiles used for taxicab service in Taiwan are not diesel-fueled, and exposure to diesel exhaust is not common in Taipei metropolitan areas. However, long-distance taxi drivers may still be exposed to diesel exhaust while stuck on the local freeways or driving into the surrounding counties where there are many diesel-powered trucks or buses running.

Other agents may also be present as causal intermediaries. For example, more time driving may increase the likelihood that a person would develop obesity, which is known to be associated with fatty liver changes, either through lack of exercise or through an unhealthy diet resulting from the necessity of eating convenience foods in order to maximize time in the taxi and profitability. Table V presents results which adjust for exercise frequency and several metabolic factors (BMI, hypertension, and diabetes), in an attempt to estimate the direct effects of long driving through non-metabolic causal pathways alone, controlling for the indirect effects of long driving that occur via the metabolic causal pathways. An additional pair of models, with cigarette smoking added to

the adjustment set used in Table V, resulted in similar effect estimates and exposure–response patterns (Supplementary Appendix Table I). The adjusted results shown in Table V support the speculated role of non-metabolic factors. However, interpretation of these results as the pure direct effects of long driving on fatty liver change via an occupational or environmental pathway relies on the strong assumption that there are no other uncontrolled or unmeasured confounders between exposure and outcome or between the causal intermediates and the outcome [Cole and Hernan, 2002].

Our study findings may have implications for research design and data analyses in studying of fatty liver disease. Since alcohol abuse is known to cause liver damage, many researchers make sharp distinctions between fatty liver disease with an alcoholic etiology and the others that are non-alcoholic related. As a result, epidemiologic studies on risk factors for fatty liver disease other than alcohol often exclude any individuals with a history of excess alcohol use from their study populations. The results reported here for ''never drinkers'' are equivalent to what would be obtained if we had used an exclusion strategy similar to that used in some other studies of liver disease [Cotrim et al., 1999, 2005; Kaukiainen et al., 2004]. However, it is important to note while the clinical classification of alcoholic versus non-alcoholic liver disease may be useful to guide treatment in clinical practice, its use as a restriction or exclusion criterion in population-based studies may be problematic [Ruhl and Everhart, 2005]. By excluding those with alcohol consumption in studies of occupational and environmental risk factors for fatty liver damages, researchers may overlook alcohol intake as a potential effect measure modifier of associations between exposures of interest and fatty liver changes and may prevent researchers from identifying subgroups that are potentially more susceptible to the hepatotoxic agents under study.

As with any cross-sectional study, the results should be interpreted as associative and not necessarily causative. This study also has several limitations. First, this study relied upon a relatively crude categorization of self-reported alcohol use history. Since alcohol is known to be hepatotoxic when abused, it would have been preferable to have more detailed information about each driver's frequency and quantity of alcohol consumption for those who identified as current drinkers, as well as data on the historical consumption patterns and period since cessation for those who reported themselves to be past drinkers. Without this information, we cannot apply criteria used by other researchers to distinguish normative alcohol use from abuse. Additionally, data on medication use were not collected, limiting our ability to adjust for potential hepatotoxicity caused by use of drugs such as non-steroidal anti-inflammatory drugs or acetaminophen, which may be of particular concern for this population because taxi drivers are at risk for work-related musculoskeletal pain [Chen et al., 2004b]. A third limitation is that for this analysis, we used a single cut-point for both genders to categorize liver enzyme elevation and selected a cut-point of <40 IU/L. There is currently some debate in the literature about whether cut-offs used for delineating ''normal'' aminotransferase levels should be lowered or made gender-specific [Clark and Diehl, 2003]. Given that our study includes few women, however, allowing for differences would likely have little effect on the findings. Additionally, some recent reports suggest that there may be a high degree of intraindividual variability in measurements of ALT [Lazo et al., 2008]. Since our study is cross-sectional and only one measurement of ALT was taken for each driver, some misclassification could be present as a result of this short-term variability. However, it is unlikely that the graded association between increasing monthly driving distance and prevalence of abnormal ALT observed in this study merely reflects the consequence of outcome misclassification. The response curve observed between driving tenure and fatty liver changes was not linear. A nonlinear pattern like the one observed could be suggestive of possible selection bias resulting from the healthy worker survivor effect; drivers who develop fatty liver disease or its sequelae as a result of their occupational exposure may have left the professional population because of diminishing health and thus not available for inclusion in this cross-section of actively employed drivers [Richardson, 2004].

The observed association between driving distance and tenure and prevalence of elevated ALT and ultrasonographically detectable fatty liver changes suggests a potentially important occupational hazard for professional drivers. If the observed interaction with alcohol use represents a true biological synergism, those who consume alcohol may be at higher risk. Further research should investigate these associations more fully, with attention to quantifying the occupational exposures plausibly related to these outcomes.

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