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Original Article

Association of nonalcoholic fatty liver and chronic kidney disease: An analysis of 37,825 cases from health checkup center in Taiwan

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Abstract

Objective: Nonalcoholic fatty liver (NAFLD) and chronic kidney disease (CKD) share common pathogenic mechanisms and risk factors. The relationship between in NAFLD and CKD remains controversial. We aim to assess the association between NAFLD and CKD. **Materials and Methods:** A cross-sectional study was based on individuals who received physical checkups at the Taipei Tzu Chi Hospital from September 5, 2005, to December 31, 2016. Demographic and clinical characteristics of the study population were collected. NAFLD was defined by abdominal ultrasonography and excluded other liver disease. CKD was defined as estimated glomerular filtration rate ≤60 mL/min/1.73 m^2 or the presence of proteinuria. The association between NAFLD and CKD was then analyzed using SAS software by using the multivariable logistic model. A higher prevalence of CKD was shown in individuals with NAFLD compared to those without NAFLD. **Results:** In univariate analysis, individuals with mild NAFLD and moderate-to-severe NAFLD were both significantly associated with CKD (odds ratio [OR], 1.23; 95% confidence interval [CI], 1.13–1.33; OR, 1.66; CI, 1.49–1.85) when compared to individuals without NAFLD. After multivariate adjustment, individuals with moderate-to-severe NAFLD were still significantly more likely to have CKD (OR, 1.17, 95% CI, 1.03–1.33). **Conclusions:** Our finding showed that the presence and severity of NAFLD was positively associated with CKD in unadjusted and adjusted analysis. Further follow-up studies may be needed to validate these associations.

Keywords: *Chronic kidney disease, Metabolic syndrome, Nonalcoholic fatty liver disease, Taiwan*

Introduction

Nonalcoholic fatty liver disease (NAFLD) became a global public health problem, and the increasing prevalence of NAFLD in Asia was also noted [1]. NAFLD is defined as the presence of ≥5% fat accumulation in liver (hepatic steatosis), in the absence of excessive alcohol consumption or other specific chronic liver diseases [2]. The prevalence of NAFLD in Taiwan is ranging from 11.4% to 41% [3,4]. The population with obesity, physical inactive, diabetes mellitus (DM), hypertension (HTN), and hyperlipidemia have a higher chance of developing NAFLD [5-7].

NAFLD is considered as the hepatic manifestation of the metabolic syndrome and shares many important metabolic risk factors and common pathogenic mechanisms with chronic kidney disease (CKD) [3,6,7] CKD is global problem and account for 8% population in the world [8]. Besides, CKD may progress to end-stage renal disease (ESRD) and is also an important cardiovascular risk factor. Taiwan has a very high prevalence of CKD which up to 11.9% [9]. Compared to the international data by using the United States Renal Data System, the incidence and prevalence of ESRD in Taiwan ranked first in the world from 2002 to 2014 [10]. Traditional risk factors of CKD include HTN, DM, obesity, age, smoking, and taking nephrotoxins [11]. In addition to traditional risk factors, metabolic syndrome and cardiovascular disease are strongly associated with CKD [12,13]. Since CKD and NAFLD have similar risk factors and pathogenic mechanisms, we hypothesized that NAFLD may be an ignored, independent risk factor of CKD. However, the direct link between CKD and NAFLD was still controversial in

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previous studies, and so far there is no large population study was conducted in Taiwan or even in Asia [7,14].

To bridge the evidence gap between NAFLD and CKD, we conducted the largest cross-sectional cohort in Taiwan. We hypothesized that NAFLD is an independent risk factor of CKD, and the severity of NAFLD is positively correlated with higher prevalence of CKD.

Materials and methods

Design and study participants

The study was designed as a cross-sectional study to investigate the association between nonalcoholic liver disease and CKD. We analyzed individuals over 40 years old who received self-paid health examinations including undergone liver ultrasonography at health check-up center of Taipei Tzu Chi Hospital (New Taipei City, Taiwan) from September 5, 2005, to December 31, 2016. We excluded individuals with missing creatinine data, inadequate imaging, individuals with viral hepatitis B or C, those who reported alcohol intake >30 g/day (male), >20 g/day (female), and those with incomplete laboratory or clinical information. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Local Ethics Committee of the institute (06-XD12-033). Informed written consent was waived because the study was a retrospective data analysis.

Clinical assessment

The structured questionnaire included questions about sex, age, medical history, and health behavior was conducted by a well training nurse. Height and weight were measured by an automatic electronic meter (SECA GM-1000, Seoul, Korea), and body mass index (BMI, kg/m^2) was calculated. We measured waist circumference (WC) at the mid-level between the lower edge of the rib cage and the iliac crest, with the participants in a standing position. A WC of ≥90 cm in men and a WC of ≥80 cm in women was classified as abdominal obesity, defined by the Health Protection Agency, Ministry of Health and Welfare, Taiwan definition [15]. An automatic blood pressure (BP) machine (Welch Allyn 53,000, NJ, USA) was used to measure BP.

Venous blood was drawn after at least 8 h of fasting. Measures included glucose, serum total cholesterol (TCH), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) (Dimension RXL Max integrated chemistry system, Siemens, Erlangen, Germany). The hemoglobin A1c (HbA1c) concentration was determined using Variant II (Bio-Rad, Richmond, CA, USA). For low HDL, there were defined as <40 mg/dL in men and <50 mg/dL in women. And for high TG, there were defined as ≥150 mg/dL [16]. Serum creatinine was measured by means of the alkaline picrate (Jaffe) method. Estimated glomerular filtration rate (eGFR) calculation was based on the CKD Epidemiology Collaboration from serum creatinine [17].

Urine protein was determined by using single dipstick analysis with an automated urine analyzer (Arkray 4030, Tokyo, Japan). These results were reported as 6-grade scale: absent (<10 mg/dL), trace (±) (10 to 20 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), or 4+ (1000 mg/dL). Patients with trace levels, 1+ level and above were defined as having proteinuria. The presence of CKD was defined as either presence of proteinuria or eGFR ≤60 mL/min per 1.73 m^2.

Liver ultrasonography was performed after at least 8 h of fasting by a well-trained specialist in gastroenterology, who was blind to participants' details using a GE Logiq S7 ultrasound machine (Seongnam-Si, Seoul, Korea). The diagnosis of fatty liver was based on the results of abdominal ultrasound including hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring. We divided three groups by ultrasound as no NAFLD, mild NAFLD, and moderate-to-severe NAFLD [18].

Statistical analysis

We compared three groups by Chi-square and one-way ANOVA on normal and continuous variables, respectively. When observe values were <5 or did not approximate to the normal distribution, the Fisher's exact tests and Kruskal–Wallis test were replaced, respectively. For the incomplete cases in this study, we used the expectation-maximization algorithm to impute and to replace each missing value except creatinine. The multiply imputed data were analyzed by using the multivariable logistic model to calculate the adjusted odds ratio (OR) and method of likelihood ratio test for model selection. To confirm the results, we also used the dataset without multiply imputed to procedure the same analysis and compare the result with multiply imputed dataset. The two-tailed test was used for statistical significance testing and $P < 0.05$ was considered statically significant. All statistical analyses carried out with SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA) and STATA 14 (StataCorp, Lakeway Dr., TX, USA).

Results

We initial enrolled 62,326 individuals and a total of 37,825 were in final analysis after exclusion criteria [Figure 1]. The clinical characteristics of the individual stratified by the presence of NAFLD and severity status are shown in Table 1.

The individuals with NAFLD were elderly, were more likely male, current smoker, higher prevalence of the history of HTN, DM, CKD, higher systolic BP, diastolic BP, higher

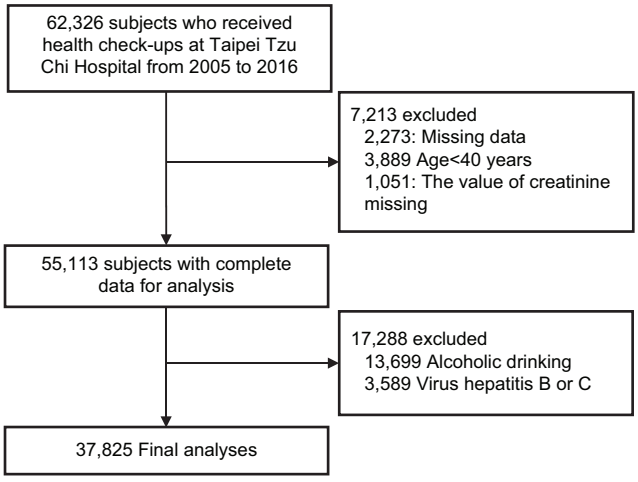

Figure 1: Flow chart of patient selection

Table 1: Characteristics of individuals according to severity of nonalcoholic fatty liver disease

	No NAFLD	Mild NAFLD	Moderate-to-severe NAFLD	*P*
n	14,616	17,229	5980	
Age (years)	58.8 (10.9)	62 (10.3)	62.1 (10.1)	<0.001
Age group, *n* (%)				
40-49	2785 (19.1)	1684 (9.8)	601 (10.1)	<0.001
50-59	4556 (31.2)	4594 (26.7)	1473 (24.6)	
60-69	4481 (30.7)	6320 (36.7)	2253 (37.7)	
≥70	2794 (19.1)	4631 (26.9)	1653 (27.6)	
Gender, *n* (%)				
Male	4492 (30.7)	6067 (35.2)	2729 (45.6)	<0.001
Female	10,124 (69.3)	11,162 (64.8)	3251 (54.4)	
Current smoking, *n* (%)	352 (2.4)	489 (2.8)	190 (3.2)	0.001
Betel chewing, *n* (%)	24 (0.2)	34 (0.2)	7 (0.1)	0.40
Comorbidity				
Diabetes, *n* (%)	582 (4.0)	1077 (6.3)	846 (14.1)	<0.001
Hypertension, *n* (%)	1808 (12.4)	3593 (20.9)	1998 (33.4)	<0.001
HbA1c (%)	5.6 (0.4)	5.7 (0.6)	6 (0.8)	<0.001
Systolic BP (mmHg)	118 (16)	122 (16)	127 (15)	<0.001
Diastolic BP (mmHg)	71 (12)	74 (12)	78 (11)	<0.001
BMI (kg/m^2)	22.3 (16.1)	23.6 (3.1)	26.7 (3.6)	<0.001
Abdominal obesity, *n* (%)	118 (0.8)	219 (1.3)	474 (7.9)	<0.001
ALT (mg/dL)	24 (21)	26 (17)	40 (37)	<0.001
Total cholesterol (mg/dL)	186 (36)	192 (37)	199 (38)	<0.001
LDL (mg/dL)	118 (30)	123 (30)	129 (31)	<0.001
Low HDL, *n* (%)	2555 (17.5)	4806 (27.9)	2658 (44.4)	<0.001
High TG, *n* (%)	1832 (12.5)	3912 (22.7)	2859 (47.8)	<0.001
Proteinuria, *n* (%)	1617 (11.1)	2201 (12.8)	900 (15.1)	<0.001
eGFR (MDRD)	87 (14)	84 (14)	83 (14)	<0.001
CKD	2027 (13.9)	2886 (16.8)	1185 (19.8)	<0.001

Data are shown as *n* (%) or mean (SD). BP: Blood pressure, BMI: Body mass index, CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate, HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, NAFLD: Nonalcoholic fatty liver disease, TG: Triglycerides, ALT: Alanine aminotransferase, SD: Standard deviation, MDRD: Modification of diet in renal disease. Abdominal obesity defined by individuals with waist circumference of ≥90 cm in men; ≥80 cm in women. CKD defined by individuals with eGFR≤60 mL/min per 1.73 m^2 or presence of proteinuria. High TG defined by individuals with triglycerides ≥150 mg/dL. Low HDL defined by individuals with HDL<40 mg/dL in men;<50 mg/dL in women

BMI or abdominal obesity, high HbA1c, high ALT, high TCH, higher LDL, higher TG, and lower HDL levels than those without NAFLD [Table 1].

Association of ultrasound-diagnosed nonalcoholic fatty liver with chronic kidney disease

We found that the percentage of CKD was higher in individuals with NAFLD compared to those without NAFLD (17.5 vs. 13.9, $P < 0.001$) [Supplement Table 1]. The highest percentage of CKD was shown in subject with moderate-to-severe NAFLD compare to those with mild or without NAFLD (19.8, 16.8 vs. 13.9; $P < 0.001$) [Table 1]. Individual with NAFLD was found to have an adjusted OR for prevalent CKD of 1.13 (95% confidence interval [CI], 1.04–1.23, $P = 0.004$) [Supplement Table 2]. As shown in Table 2, mild NAFLD and moderate-to-severe NAFLD were both significantly associated with CKD (OR, 1.23; 95% CI, 1.13–1.33; OR, 1.66; 95% CI, 1.49–1.85; $P < 0.001$) when compared to individuals without NAFLD in univariate logistic regression analysis.

In univariate logistic regression analysis, CKD was positively associated with age (OR 1.02, $P < 0.001$), male (OR 1.30, $P < 0.001$), history of HTN (OR 2.00, $P < 0.001$), DM (OR 2.11, $P < 0.001$), low HDL (OR 1.29, $P < 0.001$), high TG (OR 1.27, $P < 0.001$), and systolic BP (per 10 mmHg) (OR 1.13, $P < 0.001$). Results of the multivariate linear regression analyses were also presented in Table 2.

After adjusting sex, age, current smoking, DM, HTN, low HDL, high TG, ALT, systolic BP (per 10 mmHg) by multivariate logistic regression analysis, individuals with moderate-to-severe NAFLD were still found significantly associated with CKD. (OR, 1.17, 95% CI, 1.03–1.33, $P = 0.014$). However, individuals with mild NAFLD was no longer significant in multivariate logistic regression analysis (OR 1.05, 95% CI 0.96–1.15, $P = 0.27$) [Figure 2].

Discussion

NAFLD is increasingly recognized as the liver disease component that related to metabolic syndrome [19]. To the best of our knowledge, the present study is the largest cross-sectional cohort to date to investigate the association between NAFLD and CKD. Besides, the study was conduct in one single hospital. In this analysis, we found a significant, positive association between NAFLD and CKD in univariate analysis. Moreover, increasing severity of NAFLD, the prevalence of CKD was increasing. The association still remains significantly in individuals with moderate-to-severe NAFLD, after we adjusted age,

Table 2: Univariate and multivariate analysis of the presence of chronic kidney disease

Variable	CKD, *n* (%)		Univariate analysis		Multivariate analysis	
	Yes (*n*=6098)	No (*n*=31,727)	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)	-	-	1.02 (1.02-1.02)	<0.001	1.01 (1.00-1.01)	<0.001
Gender (male)	2520	10,768	1.30 (1.21-1.40)	<0.001	1.26 (1.16-1.37)	<0.001
Current smoking	239	792	1.10 (0.94-1.28)	0.24	1.53 (1.25-1.87)	<0.001
Diabetes	806	1699	2.11 (1.87-2.38)	<0.001	1.51 (1.32-1.73)	<0.001
Hypertension	1993	5406	2.00 (1.85-2.17)	<0.001	1.44 (1.31-1.59)	<0.001
Abdominal obesity	172	639	-	-	-	-
Systolic BP (per 10 mmHg)	-	-	1.13 (1.10-1.15)	<0.001	1.00 (0.99-1.00)	0.004
ALT (mg/dL)	-	-	1.00 (1.00-1.00)	0.3	1.00 (0.99-1.00)	0.009
Total cholesterol (mg/dL)	-	-	1.00 (1.00-1.00)	0.37	-	-
Low HDL	2119	7900	1.29 (1.20-1.39)	<0.001	1.03 (0.95-1.13)	0.47
High TG	1669	6934	1.27 (1.17-1.38)	<0.001	1.12 (1.01-1.24)	0.036
No NAFLD	2027	12,589	1.0 (reference)	-	1.0 (reference)	-
Mild NAFLD	2886	14,343	1.23 (1.13-1.33)	<0.001	1.05 (0.96-1.15)	0.27
Moderate-to-severe NAFLD	1185	4795	1.66 (1.49-1.85)	<0.001	1.17 (1.03-1.33)	0.014

BP: Blood pressure, HDL: High-density lipoprotein, NAFLD: Nonalcoholic fatty liver disease, TG: Triglyceride, ALT: Alanine aminotransferase, OR: Odds ratio, CI: Confidence interval, CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate. Abdominal obesity defined by individuals with waist circumference of ≥90 cm in men; ≥80 cm in women. CKD defined by individuals with eGFR ≤60 mL/min per 1.73 m^2 or presence of proteinuria. High TG defined by individuals with triglycerides ≥150 mg/dL. Low HDL defined by individuals with HDL <40 mg/dL in men; <50 mg/dL in women

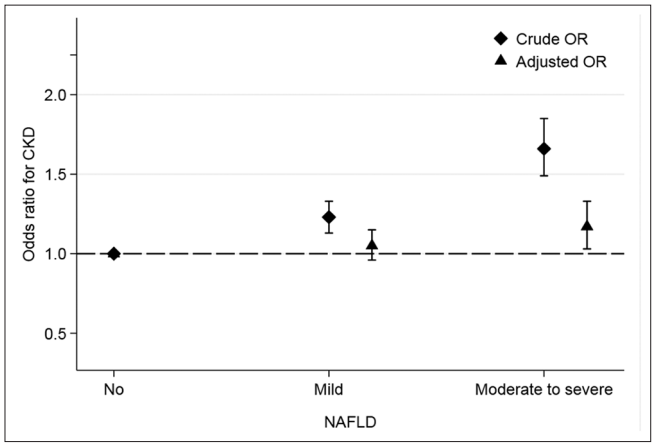

Figure 2: Odds of prevalent CKD in individuals with different severity of NAFLD as compared to individuals without NAFLD. CKD: Chronic kidney disease, NAFLD: Nonalcoholic fatty liver disease

sex, current smoking, DM, HTN, low HDL, high TG, ALT, and systolic BP. The higher prevalence of CKD was shown in individuals with NAFLD compared to without NAFLD.

Recent observational studies have demonstrated the positive association between NAFLD and CKD across diabetes or nondiabetes population [6,20-23]. However, in another large cross-sectional study in the US among 11,469 adults from NHANES showed ultrasound-diagnosed NAFLD is not associated with prevalent of CKD after adjusting cardiometabolic factors (OR 1.04, 95% CI 0.88–1.23, P = 0.64). Besides, no significant relationship between NAFLD severity and prevalent CKD was found after adjusting cardiometabolic factors [7]. On the contrary, we found that the presence of NAFLD was positively associated with the prevalence of CKD by multivariate analysis in our study (OR 1.13, 95% CI 1.04–1.23, P = 0.004). Likewise, individuals with moderate-to-severe NAFLD remain significantly associated with prevalent of CKD (adjusted OR 1.17, 95% CI 1.03-1.33, P = 0.014). This difference may be attributed to ethnic differences or different causes of CKD. A meta-analysis including 33 studies (20 cross-sectional and 13 longitudinal studies, including nearly 64,000 individuals) concluded the presence and severity of NAFLD are associated significant with CKD in 2014 (OR 2.12, 95% CI 1.69–2.66) [24]. However, the heterogeneity of definition of NAFLD included histology, imaging, or liver enzyme elevation. On the contrary, we used only sonography for the diagnosis of NAFLD in our study.

Although the definitive mechanism between NAFLD and CKD was not fully understood, many risk factors for NAFLD have influenced the development of CKD. Growing evidence suggest that they shared common pathogenetic mechanisms and may be cross-link each other. In individuals with NAFLD, increasing visceral obesity and insulin resistance causes the release of pro-inflammatory cytokines (interleukin-6, tumor necrosis factor-alpha, and C-reactive protein) and worsens renal hemodynamic that contributes to the progression of kidney disease [25-28]. Furthermore, atherogenic dyslipidemia and increasing level of procoagulant with profibrogenic mediators (fibrinogen, factor VII, and tissue factor) are common in patient with NAFLD, that cause atherosclerotic vascular disease and renal vascular damage [29-32].

Some limitations of this study must also be acknowledged. First, our individuals selected from health check-up in one medical center may not be representative of the general population due to possible selection bias. Second, we used ultrasound to detect NAFLD, but not confirmed by liver biopsy. However, ultrasound is safe and noninvasive way to detect NAFLD for the general population. Third, this study had a cross-sectional design, so the causal relationship could not be established between a NAFLD and CKD.

Conclusions

Our finding showed that the presence and severity of NAFLD was significant, positive association with CKD in

unadjusted and adjusted analysis. We still need further studies to define mechanisms that link NAFLD and CKD.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplement Table 1: Characteristics of individuals according to nonalcoholic fatty liver disease

	No NAFLD	NAFLD	*P*
n	14,616	23,209	<0.001
Age (years)	58.8 (10.9)	62 (10.2)	<0.001
Age group, *n* (%)			
40-49	2785 (19.1)	2285 (9.8)	<0.001
50-59	4556 (31.2)	6067 (26.1)	<0.001
60-69	4481 (30.7)	8573 (36.9)	<0.001
≥70	2794 (19.1)	6284 (27.1)	<0.001
Gender, *n* (%)			
Male	4492 (30.7)	8796 (37.9)	<0.001
Female	10,124 (69.3)	14,413 (62.1)	<0.001
Current smoking, *n* (%)	352 (2.4)	679 (2.9)	0.003
Betel chewing, *n* (%)	24 (0.2)	41 (0.2)	0.78
Comorbidity			
Diabetes, *n* (%)	582 (4.0)	1923 (8.3)	<0.001
Hypertension, *n* (%)	1808 (12.4)	5591 (24.1)	<0.001
HbA1c (%)	5.6 (0.4)	5.8 (0.7)	<0.001
Systolic BP (mmHg)	118 (16)	123 (16)	<0.001
Diastolic BP (mmHg)	71 (12)	75 (12)	<0.001
BMI (kg/m^2)	22.3 (16.1)	24.4 (3.5)	<0.001
Abdominal obesity, *n* (%)	118 (0.8)	693 (3.0)	<0.001
ALT (mg/dL)	24 (21)	29 (24)	<0.001
Total cholesterol (mg/dL)	186 (36)	194 (37)	<0.001
LDL (mg/dL)	118 (30)	126 (16)	<0.001
Low HDL, *n* (%)	1832 (12.5)	6771 (29.2)	<0.001
High TG, *n* (%)	2555 (17.5)	7464 (32.2)	<0.001
Proteinuria, *n* (%)	392 (2.7)	821 (3.5)	<0.001
eGFR (MDRD)	87 (14)	84 (14)	<0.001
CKD	2027 (13.9)	4071 (17.5)	<0.001

Data are shown as *n* (%) or mean (SD). BP: Blood pressure, BMI: Body mass index, CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate, HbA1c: Hemoglobin A1c, NAFLD: Nonalcoholic fatty liver disease, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglycerides, ALT: Alanine aminotransferase, SD: Standard deviation, MDRD: Modification of diet in renal disease. Abdominal obesity defined by individuals with waist circumference of ≥90 cm in men; ≥80 cm in women. CKD defined by individuals with eGFR <60 mL/min per 1.73 m^2 or proteinuria. High TG defined by individuals with triglycerides ≤150 mg/dL. Low HDL defined by individuals with HDL <40 mg/dL in men; <50 mg/dL in women

Supplement Table 2: Univariate and multivariate analysis of the presence of chronic kidney disease

Variable	CKD, *n* (%)		Univariate analysis		Multivariate analysis	
	Yes (*n*=6098)	No (*n*=31,727)	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)	-	-	1.03 (1.03-1.03)	<0.001	1.01 (1.01-1.01)	<0.001
Gender (male)	2520	10,768	1.37 (1.30-1.45)	<0.001	1.27 (1.17-1.38)	<0.001
Current smoking	239	792	1.59 (1.38-1.85)	<0.001	1.54 (1.27-1.88)	<0.001
Diabetes	806	1699	2.69 (2.46-2.94)	<0.001	1.54 (1.35-1.76)	<0.001
Hypertension	1993	5406	2.36 (2.22-2.51)	<0.001	1.46 (1.33-1.61)	<0.001
Abdominal obesity	172	639	1.41 (1.19-1.68)	<0.001	-	-
Systolic BP (per 10 mmHg)	-	-	1.61 (1.51-1.70)	<0.001	1.09 (1.00-1.19)	0.049
ALT (mg/dL)	-	-	1.35 (1.27-1.43)	<0.001	1.10 (1.00-1.22)	0.06
Total cholesterol (mg/dL)	-	-	1.00 (1.00-1.00)	0.12	1.00 (1.00-1.00)	0.021
Low HDL	2119	7900	1.00 (1.00-1.00)	0.91	-	-
High TG	1669	6934	1.30 (1.25-1.35)	<0.001	-	-
No NAFLD	2027	12,589	1.0 (reference)	-	1.0 (reference)	-
NAFLD	4071	19,138	1.32 (1.25-1.40)	<0.001	1.13 (1.04-1.23)	0.004

BP: Blood pressure, HDL: High density lipoprotein, NAFLD: Nonalcoholic fatty liver disease, TG: Triglyceride, eGFR: Estimated glomerular filtration rate, HDL: High-density lipoprotein, OR: Odds ratio, CI: Confidence interval, ALT: Alanine aminotransferase, CKD: Chronic kidney disease. Abdominal obesity defined by individuals with waist circumference of ≥90 cm in men; ≥80 cm in women. CKD defined by individuals with eGFR ≤60 mL/min per 1.73 m^2 or presence of proteinuria. High TG defined by individuals with triglycerides ≥150 mg/dL. Low HDL defined by individuals with HDL <40 mg/dL in men; <50 mg/dL in women