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# Nonalcoholic fatty liver disease predicts chronic kidney disease in nonhypertensive and nondiabetic Korean men

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**Abstract**

In the absence of significant research, we performed a prospective study to examine the association between nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD). The study cohort comprised a total of 8329 healthy men, with normal baseline kidney functions and no proteinuria, working in a semiconductor manufacturing company and its 13 affiliates. Alcohol intake was assessed with a self-reported questionnaire. Biochemical tests for liver and metabolic function and abdominal ultrasonography were done. *Chronic kidney disease* was defined as either the presence of proteinuria or a glomerular filtration rate (GFR) of <60 mL/min per 1.73 $m^2$. Cox proportional hazards model was used to estimate hazard ratios in the model for CKD. During 26 717.1 person-years of follow-up, 324 men developed CKD. Nonalcoholic fatty liver disease was associated with the development of CKD (crude relative risk, 2.18; 95% confidence interval [CI], 1.75-2.71); and this relationship remained significant even after adjustment for age, GFR, triglyceride, and high-density lipoprotein cholesterol (adjusted relative risk [aRR], 1.55; 95% CI, 1.23-1.95). The association between NAFLD and incident CKD was evident in the NAFLD group with elevated serum γ-glutamyltransferase (GGT) (aRR, 2.31; 95% CI, 1.53-3.50), even after adjustment for age, GFR, triglyceride, and high-density lipoprotein cholesterol, but not in the NAFLD group without elevated GGT (aRR, 1.09; 95% CI, 0.79-1.50) ($P$ = .008 for interaction). To summarize, NAFLD with elevated GGT concentration was associated with an increased CKD risk among nondiabetic, nonhypertensive Korean men, irrespective of metabolic syndrome.


## 1. Introduction

Hepatic steatosis unrelated to excessive alcohol consumption is termed *nonalcoholic fatty liver disease* (NAFLD), which is increasingly recognized as a major cause of liver-related morbidity and mortality [1]. Moreover, multiple lines of evidence link NAFLD with obesity, diabetes, dyslipidemia, and hypertension, which are the main features of the recently characterized metabolic syndrome (MetS) [2-5]. Excessive fat deposits in nonadipose tissue such as the liver may be a sign of failure of the system that normally acts "by confining the lipid overload to cells specifically designed to store large quantities of surplus calories, the white adipocytes" [6]. Studies have shown that among the measures of adiposity, the percentage of hepatic fat was the parameter best correlated with the insulin resistance, even in subjects with normal glucose tolerance and, accordingly, that NAFLD might represent another feature of MetS [4,7]. Therefore, NAFLD could be a phenotype of excessive adiposity beyond the normal liporegulation [6] and also may be regarded as one of the components of MetS [7,8].

Recently, several studies have reported that MetS and insulin resistance were associated with an increased risk for chronic kidney disease (CKD) [9-12]. The aforementioned interrelations between NAFLD, insulin resistance, and MetS raise the possibility that NAFLD can predict the development of CKD. However, there are sparse data on

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the relationships among NAFLD and CKD risk in apparently healthy persons. This is important because the incidence of both NAFLD and CKD is increasing worldwide [1,13].

Therefore, the present prospective study examined the association between NAFLD and CKD risk in nonhypertensive and nondiabetic Korean male workers. We also examined whether the relationship between NAFLD and CKD risk was modified by elevated hepatic enzyme concentrations.

## 2. Methods

### 2.1. Subjects

The study population was composed of Korean male workers of one of the largest semiconductor manufacturing companies in Korea and its 13 affiliates [14]. All of the workers were required to participate in either annual or biennial health examinations by the Industrial Safety and Health Law in Korea. In 2002, 15 347 workers, aged 30 to 59 years, participated in the comprehensive health examinations at a university hospital in Seoul, Korea. A total of 5964 men were excluded based on the following exclusion criteria that might influence kidney function or ultrasonography (US) findings of the liver as a result of other liver disease: 27 had a history of malignancy; 16 had a history of cardiovascular disease; 125 reported current uses of blood lipid–lowering agents; 279 had a fasting glucose level of ≥126 mg/dL or current use of blood glucose–lowering agents; 2688 were taking medication for hypertension or had a blood pressure of ≥140/90 mm Hg; 11 took an antiviral drug for chronic active hepatitis; 841 had a positive serologic finding for either hepatitis B or C virus, a reported history of known liver diseases, a recent use of medication that could influence steatosis, or abnormal liver US findings of chronic liver disease, liver cirrhosis, intrahepatic or extrahepatic cholelithiasis, and abnormal dilatation of biliary tree; 7 were taking medication for current kidney disease; 260 had a dipstick-positive proteinuria; 261 had a glomerular filtration rate (GFR) of <60 mL/min per 1.73 $m^2$; 2498 had alcohol intake of ≥20 g/d, which is the currently accepted cutoff level in the diagnosis of NAFLD [1]; and 337 had missing data on information of their medical histories, urinalysis, or serum aminotransferase levels. Because some individuals were excluded for multiple reasons, the total number of eligible subjects for the study was 9383.

This CKD-free cohort was reexamined at the same hospital for 4 consecutive years until October 2006. We excluded an additional 1054 subjects from our cohort who did not participate in follow-up examinations. Accordingly, 8329 male workers (88.5%) were included in the final analysis and were observed for the development of CKD (with a mean follow-up period [SD]) of 3.21 [1.01] years). This study was approved by the Institutional Review Board at Kangbuk Samsung Hospital.

### 2.2. Measurements

The initial health examinations in 2002 included a medical history, physical examination, questionnaire on health-related behavior, and anthropometric and biochemical measurements. The medical history and history of prescription drug use were assessed by the examining physicians. All participants were asked to respond to a questionnaire on health-related behavior. Questions about alcohol intake included the frequency of alcohol consumption on a weekly basis and the usual amount that was consumed on a daily basis. We considered persons reporting that they smoked to be current smokers. In addition, participants were asked about their weekly frequency of physical activity such as jogging, bicycling, and swimming that lasted long enough to produce perspiration.

The blood specimens were sampled from an antecubital vein after more than 12 hours of fasting. The serum levels of fasting glucose, total cholesterol, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), γ-glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were measured using the Bayer Reagent Packs on an automated chemistry analyzer (ADVIA 1650 Autoanalyzer; Bayer HealthCare, Tarrytown, NY). The principles of the measurement were hexokinase method for glucose; enzymatic colorimetric assay for LDL-C, HDL-C, total cholesterol, and TG; and immunoradiometric assay (Biosource, Nivelles, Belgium) for insulin. Insulin resistance was assessed with the homeostasis model assessment of insulin resistance (HOMA-IR): fasting blood insulin (in microunits per milliliter) × fasting blood glucose (in millimoles per liter)/22.5. High-sensitivity C-reactive protein (hsCRP) was analyzed by particle-enhanced immunonephelometry with the BN II System (Dade Behring, Malburg, Germany). The serum creatinine was measured by means of the alkaline picrate (Jaffe) method. The within-run and total coefficients of variation for creatinine determinations were no greater than 3% from 2002 to 2006. The clinical laboratory has participated in the inspection and survey by the Korean Association of Quality Assurance for Clinical Laboratories annually and has been verified for its level of quality control and performance of various measurements.

Urine protein was determined at each examination by the single urine dipstick semiquantitative analysis (URiSCAN Urine Strip; YD Diagnostics, Yong-In, Korea). Dipstick urinalysis was performed on fresh, midstream urine samples collected in the morning. The amount of urine protein was reported as 6 grades, absent, trace, 1+, 2+, 3+, and 4+, which corresponded to the protein levels of about undetectable, 10, 30, 100, 300, and 1000 mg/dL, respectively. *Proteinuria* was defined as grades of 1+ or greater.

Glomerular filtration rate was estimated by using the simplified Modification of Diet in Renal Disease Study [15] equation, as recommended by the National Kidney Foundation [13]: GFR (in milliliters per minute per 1.73 square meters

body surface area) = 186.3 × (serum creatinine)$^{-1.154}$ × age$^{-0.203}$. *Chronic kidney disease* was defined as either proteinuria or GFR <60 mL/min per 1.73 m$^2$.

Trained nurses measured sitting blood pressure levels with a standard mercury sphygmomanometer. Height and weight were measured after an overnight fast with the subjects wearing a lightweight hospital gown and no shoes.

The diagnosis of fatty liver was based on the results of abdominal US with a 3.5-MHz transducer (Logic Q700 MR; GE, Milwaukee, WI). The US was carried out by 3 experienced radiologists who were unaware of the aims of the study and blinded to laboratory values [16]. Of the 4 known criteria (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring [17]), the participants were required to have hepatorenal contrast and liver brightness to be diagnosed with fatty liver. Vascular blurring (blurring of the hepatic vein) and deep attenuation (attenuation of the echo level in the deep region of the liver) were also present in many cases, but their absence did not exclude the diagnosis.

The Adult Treatment Panel III proposed the following 5 abnormalities to define MetS [18]: (1) abdominal obesity; (2) high fasting glucose ≥110 mg/dL; (3) hypertriglyceridemia: TG ≥150 mg/dL; (4) low HDL-C: HDL-C <40 mg/dL; and (5) high blood pressure: ≥130/85 mm Hg. Because waist measurements were not available for the entire study sample, we substituted a body mass index (BMI) ≥25 kg/m$^2$ for all subjects as an index of obesity because this cutoff has been proposed for the diagnosis of obesity in Asian people [19]. Subjects with 3 or more of the above 5 abnormalities were considered to have MetS.

### 2.3. Statistical analysis

The data were represented as estimated means (95% confidence interval [CI]) or adjusted proportion (95% CI) after adjustment for age and BMI. Group comparisons in means and percentages among the characteristics of the study participants by the presence of NAFLD were tested by analysis of variance adjusted for age and BMI or by the Mantel-Haenszel method for categorical variables adjusted for age and BMI. The distributions of continuous variables were evaluated, and transformations were used in the analysis as required. Incidence density was expressed as the number of cases divided by the person-years from the baseline until an assumed time of CKD development in the middle of the follow-up period or until the final examination. Incidence densities were compared by calculating the incidence density ratios with the 95% CI. Cox proportional hazards model was used to calculate the adjusted hazard ratios in the model for CKD. We confirmed that the proportional hazards assumption was not violated for NAFLD and risk for CKD by using a graph of estimated In(−In) survival, stratified by the presence of NAFLD [20]. The data were adjusted, first for age alone, then for the multiple covariates. In the multivariate models, we included the following variables that might confound the relation between NAFLD and CKD: age, baseline GFR, BMI, fasting serum glucose, systolic blood pressure, TG, HDL-C, HOMA-IR, hsCRP, smoking, alcohol consumption, incident diabetes, and incident hypertension. We also checked for the effect modification of the NAFLD-CKD relation by including interaction form for MetS, HOMA-IR, hsCRP, and hepatic enzymes. Their elevated levels except MetS were defined as values in their respective highest quartiles in this study population. We also cross-analyzed our data using the 40-U/L cutoff, which is comparable with the top quartile of a previous study population [14]. This analysis did not qualitatively change any of the results presented in this study; therefore, we elected to report our analysis with their respective top quartile. The data were analyzed, and the statistical analysis for the data was performed with SPSS version 13.0 software (SPSS, Chicago, IL). All the reported *P* values were 2-tailed, and those < .05 were considered to be statistically significant.

## 3. Results

At baseline, mean (SD, range) age and BMI of the 8329 subjects were 36.7 years (4.8, 30-59) and 23.8 kg/m$^2$ (2.7, 15.1-37.3), respectively. There were no differences in baseline variables except age between those lost to follow-up and those with successful follow-up (the former group was 0.4 years older than the latter group) (data not shown).

Table 1 shows the characteristics of the study participants classified according to presence of NAFLD. Of the 8329 subjects, 2516 (30.2%) had NAFLD on US at baseline. These NAFLD subjects were older, more likely to have MetS, and less likely to drink alcohol than those without NAFLD. Body mass index, glucose, total cholesterol, TG, LDL-C, hepatic enzymes, and creatinine were positively associated with NAFLD, whereas HDL-C, light drinking, and regular exercise were inversely associated with NAFLD. The overall prevalence of obesity (BMI ≥25 kg/m$^2$) was 32.8%. The prevalence of NAFLD was 56.2% in obese subjects and 17.6% in nonobese subjects.

Table 2 shows the distributions of metabolic profiles according to the number of MetS traits by the presence of NAFLD. Tests for differences of variables across the number of MetS traits found that BMI, glucose, blood pressure, HDL-C, TG, HOMA-IR, ALT, and GGT showed a linear trend across the number of MetS traits in both subjects with NAFLD and those without. Interestingly, except diastolic blood pressure, these metabolic profiles were higher in subjects with NAFLD than in those without NAFLD, irrespective of the number of MetS traits.

During 26717.1 person-years of follow-up, 324 new incident cases of CKD developed. The crude relative risk for CKD in subjects with NAFLD, compared with those without, was 2.18 (95% CI, 1.75-2.71); and this relationship remained significant even after adjustment for age, GFR, hypertriglyceridemia, and low HDL-C (adjusted relative risk

Table 1
Estimated[a] mean values (95% CI) and adjusted[a] proportion (95% CI) of baseline characteristics of study participants according to the presence of NAFLD

| | Non-NAFLD on US (n = 5813) | NAFLD on US (n = 2516) | *P* value |
|---|---|---|---|
| Age (y) | 36.6 (36.5-36.7) | 37.0 (36.8-37.2) | .001 |
| BMI (kg/m$^2$) | 23.0 (22.9-23.0) | 25.7 (25.6-25.8) | <.001 |
| FBS (mg/dL) | 90.1 (89.8-90.3) | 92.0 (91.6-92.3) | <.001 |
| Systolic BP (mm Hg) | 111.9 (111.7-112.1) | 112.1 (111.7-112.5) | .347 |
| Diastolic BP (mm Hg) | 71.9 (71.7-72.1) | 72.2 (71.9-72.5) | .167 |
| TC (mg/dL) | 197.9 (197.0-198.7) | 207.7 (206.3-209.1) | <.001 |
| HDL-C (mg/dL) | 52.3 (52.0-52.6) | 49.5 (49.0-49.9) | <.001 |
| LDL-C (mg/dL) | 118.9 (118.1-119.6) | 124.1 (122.9-125.3) | <.001 |
| TG (mg/dL) | 133.2 (130.9-135.5) | 177.0 (173.3-180.7) | <.001 |
| ALT (U/L) | 26.3 (25.7-26.8) | 43.5 (42.7-44.4) | <.001 |
| AST (U/L) | 23.7 (23.4-23.9) | 29.2 (28.8-29.6) | <.001 |
| ALP (U/L) | 56.0 (55.7-56.4) | 58.5 (57.9-59.0) | <.001 |
| GGT (U/L) | 28.0 (27.5-28.6) | 37.2 (36.3-38.1) | <.001 |
| Creatinine (mg/dL) | 1.13 (1.12-1.13) | 1.13 (1.13-1.14) | .045 |
| GFR (mL/min per 1.73 m$^2$) | 79.2 (79.0-79.5) | 78.9 (78.5-79.3) | .139 |
| Insulin (*m*U/dL) | 7.18 (7.12-7.25) | 8.39 (8.28-8.49) | <.001 |
| HOMA-IR | 1.61 (1.59-1.62) | 1.92 (1.90-1.95) | <.001 |
| hsCRP (mg/L) | 1.00 (0.96-1.05) | 1.15 (1.07-1.22) | .001 |
| Current smoker (%) | 45.1 (43.8-46.4) | 42.2 (40.0-44.5) | .086 |
| Light drinker (%)[b] | 28.0 (26.7-29.2) | 23.0 (21.2-24.9) | <.001 |
| Obesity (%)[c] | 20.6 (19.5-21.6) | 61.1 (59.2-63.0) | <.001 |
| MetS (%) | 5.1 (4.4-5.8) | 9.7 (8.8-10.5) | <.001 |

Data are estimated mean values (95% CI) or adjusted proportion (95% CI). FBS indicates fasting serum glucose; BP, blood pressure; TC, total cholesterol.

[a] Adjusted for age and BMI.

[b] 10~20 g of alcohol per day.

[c] BMI ≥25 kg/m$^2$.

[aRR], 1.55; 95% CI, 1.23-1.95). These associations remained significant, although the relations were attenuated after any one of BMI, HOMA-IR, or hsCRP was added to the above model. To explore whether the CKD risk in relation to NAFLD was mediated by MetS or not, we fit additional models to adjust for MetS. The adjustment for MetS had no differential effect on the associations between NAFLD and CKD risk (Table 2). Over 3.2 years of follow-up, 122 subjects (1.5% of the cohort) developed incident diabetes, 1146 (13.9%) developed hypertension, and 1204 (14.5%) developed MetS. The association between NAFLD and CKD risk remained significant after additional adjustment for incident diabetes, incident hypertension, or incident MetS. In addition, to explore whether the risk for CKD was mediated by the subsequent increase of alcohol intake, we fit an additional model, excluding participants who reported ethanol intake of ≥20 g/d at any follow-up. Even after these exclusions, the association between NAFLD and CKD remained statistically significant (data not shown).

The associations of NAFLD with CKD risk, classified according to the presence of MetS, or in each highest quartile of variables including HOMA-IR, hsCRP and hepatic enzymes, are presented in Table 3. The association between NAFLD and incident CKD was more evident in the NAFLD group with elevated GGT (aRR, 2.31; 95% CI, 1.53-3.50) than in the NAFLD group without elevated GGT (aRR, 1.09; 95% CI, 0.79-1.50) ($P = .008$ for interaction). Except for GGT, there were no significant interactions of other variables on the associations between NAFLD and CKD risk (Table 4).

## 4. Discussion

In the present prospective study of nonhypertensive and nondiabetic Korean men, NAFLD was associated with an increased CKD risk. Previous studies have suggested that MetS is associated with CKD development [9,10,12]. Similarly, in our prospective studies, MetS was an independent predictor of CKD incidence. Furthermore, our study showed that NAFLD was associated with an increased CKD risk, even in participants without MetS.

The mechanisms by which NAFLD increases CKD risk are yet to be elucidated. However, there might be several explanations underlying the effects of NAFLD on CKD. There is increasing evidence that obesity (visceral adiposity) may damage the kidney in otherwise healthy subjects [21-23]. Nonalcoholic fatty liver disease as a phenotype of excessive adiposity beyond normal liporegulation might be associated with CKD. Currently, the importance of NAFLD and its relationship to the MetS is increasingly recognized [7,8]. In our study, NAFLD was associated with all MetS components; and an association between NAFLD and CKD risk remained after adjustment for MetS. These relationships were observed even in nonhypertensive and nondiabetic participants without MetS and were independent of insulin resistance assessed by HOMA-IR. In addition, our study showed that metabolic profiles, hsCRP, and HOMA-IR were more deteriorated in subjects with NAFLD than in those without NAFLD, irrespective of MetS traits. Several experimental findings have shown that hepatic insulin resistance plays a dominant role in the pathophysiologic cascade initiated by obesity [24] and that it could activate the abnormal metabolic matrix [25]. Evidence is now accumulating that NAFLD may be a marker of cardiovascular disease, as well as being involved in its pathogenesis [26,27]. Therefore, NAFLD, either as another feature of MetS or as a phenotype of insulin resistance (ie, hepatic insulin resistance or more severe insulin resistance), might be associated with CKD incidence as a type of cardiovascular disease.

Whereas a previous study showed that low-grade inflammation assessed by hsCRP might be a predictor for a change in kidney function in the elderly [28], our results derived from apparently healthy subjects showed that hsCRP was not independently associated with incident CKD. Although the selection of healthy subjects might have attenuated the relationship between all risk factors and CKD, a significant relationship of NAFLD with incident CKD was still demonstrated.

With respect to the relation between GGT and renal disease, a previous study showed that serum GGT was

Table 2
Distributions of metabolic profiles according to the number of MetS traits by the presence of NAFLD (n =8329)

| | | No. of MetS traits | | | | *P* for trend[a] | *P* value[b] |
|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | ≥ 3 | | |
| BMI (kg/m$^2$) | No NAFLD | 21.9 (21.8-21.9) | 23.7 (23.6-23.8) | 25.1 (25.0-25.3) | 26.2 (25.9-26.5) | <.001 | <.001 |
| | NAFLD | 23.2 (23.0-23.4) | 25.2 (25.1-25.4) | 25.6 (26.5-26.7) | 27.3 (27.1-27.5) | <.001 | |
| FBS (mg/dL) | No NAFLD | 88.7 (88.4-89.0) | 90.0 (89.5-90.4) | 91.6 (90.9-92.3) | 93.8 (92.5-95.1) | <.001 | <.001 |
| | NAFLD | 90.9 (89.9-91.9) | 91.8 (91.1-92.4) | 93.3 (92.7-94.0) | 96.8 (95.9-97.8) | <.001 | |
| Systolic BP (mm Hg) | No NAFLD | 109.1 (108.8-109.5) | 113.2 (112.8-113.6) | 115.4 (114.7-116.1) | 118.8 (117.5-120.1) | <.001 | .006 |
| | NAFLD | 110.6 (109.7-111.6) | 111.9 (111.3-112.6) | 113.3 (112.7-113.9) | 117.4 (116.5-118.3) | <.001 | |
| Diastolic BP (mm Hg) | No NAFLD | 70.6 (70.3-70.9) | 72.5 (72.1-72.8) | 73.1 (72.5-73.7) | 73.4 (72.3-74.5) | <.001 | .770 |
| | NAFLD | 71.9 (71.1-72.6) | 72.9 (72.4-73.4) | 72.9 (72.4-73.4) | 74.4 (73.7-75.1) | <.001 | |
| HDL-C (mg/dL) | No NAFLD | 56.7 (52.3-57.1) | 51.3 (50.8-51.8) | 45.9 (45.1-46.7) | 39.5 (38.0-41.1) | <.001 | <.001 |
| | NAFLD | 54.7 (53.8-55.6) | 50.4 (49.8-51.0) | 45.9 (45.3-46.5) | 38.5 (37.7-39.4) | <.001 | |
| TG (mg/dL) | No NAFLD | 89.0 (87.8-90.3) | 133.2 (130.8-135.5) | 181.5 (176.4-186.6) | 217.9 (206.4-230.0) | <.001 | <.001 |
| | NAFLD | 94.8 (91.1-98.6) | 145.6 (141.9-149.5) | 207.5 (202.4-212.7) | 264.5 (254.9-274.5) | <.001 | |
| HOMA-IR | No NAFLD | 1.35 (1.33-1.37) | 1.49 (1.46-1.51) | 1.58 (1.54-1.62) | 1.71 (1.63-1.79) | <.001 | <.001 |
| | NAFLD | 1.77 (1.71-1.83) | 1.91 (1.87-1.95) | 2.05 (2.00-2.10) | 2.18 (2.11-2.25) | <.001 | |
| hsCRP (mg/L) | No NAFLD | 0.49 (0.47-0.51) | 0.50 (0.48-0.52) | 0.56 (0.52-0.61) | 0.57 (0.49-0.66) | .023 | .004 |
| | NAFLD | 0.82 (0.75-0.91) | 0.77 (0.72-0.82) | 0.80 (0.75-0.85) | 0.77 (0.77-0.92) | .356 | |
| ALT (U/L) | No NAFLD | 21.1 (20.8-21.4) | 23.3 (22.9-23.7) | 24.5 (23.7-25.3) | 25.33 (23.8-26.8) | <.001 | <.001 |
| | NAFLD | 35.4 (33.5-37.3) | 39.8 (38.4-41.2) | 42.2 (40.8-43.6) | 45.6 (43.4-48.0) | <.001 | |
| GGT (U/L) | No NAFLD | 20.5 (20.1-20.9) | 23.5 (22.9-24.0) | 25.8 (24.8-26.8) | 27.4 (25.5-29.5) | <.001 | <.001 |
| | NAFLD | 28.5 (27.0-30.1) | 34.7 (33.4-35.9) | 37.0 (35.7-38.3) | 41.6 (39.5-43.8) | <.001 | |
| GFR (mL/min per 1.73 m$^2$) | No NAFLD | 79.8 (79.5-80.2) | 79.7 (79.3-80.1) | 79.1 (78.4-79.8) | 80.4 (79.0-81.7) | .462 | .141 |
| | NAFLD | 78.6 (77.5-79.7) | 78.5 (77.8-79.2) | 76.8 (76.1-77.5) | 77.4 (76.4-78.4) | .004 | |

Data are mean values (95% CI) adjusted for age and BMI, but BMI was adjusted for only age.

[a] For analyzing the linear trends, the number of MetS traits was used as a continuous variable instead of being represented as a dummy variable and tested on each linear regression model.

[b] *P* value between the group with NAFLD and that without.

Table 3
Adjusted relative risk of incidence of CKD

| | Age-adjusted RR (95% CI) | Multivariate-adjusted RR (95% CI) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
| Age per 1-y increment | 1.12 (1.10-1.14) | 1.09 (1.07-1.11) | 1.08 (1.06-1.10) | 1.08 (1.06-1.10) | 1.08 (1.06-1.10) | 1.08 (1.05-1.10) | 1.08 (1.06-1.11) |
| NAFLD | 2.08 (1.67-2.59) | 1.55 (1.23-1.95) | 1.49 (1.18-1.88) | 1.44 (1.12-1.84) | 1.42 (1.12-1.81) | 1.41 (1.10-1.80) | 1.60 (1.27-2.01) |
| GFR per 1-SD increment | 0.41 (0.36-0.47) | 0.43 (0.37-0.49) | 0.43 (0.37-0.49) | 0.43 (0.37-0.49) | 0.43 (0.37-0.49) | 0.44 (0.38-0.51) | 0.42 (0.37-0.49) |
| Obesity[a] | 1.81 (1.46-2.25) | | | 1.11 (0.87-1.42) | | | |
| Impaired fasting glucose[b] | 1.61 (0.90-2.87) | | | | | | |
| Prehypertension[c] | 1.14 (0.78-1.66) | | | | | | |
| Low HDL[d] | 1.84 (1.41-2.39) | 1.53 (1.16-2.01) | 1.54 (1.17-2.02) | 1.53 (1.16-2.01) | 1.51 (1.15-1.99) | 1.58 (1.18-2.11) | |
| High TG[e] | 2.20 (1.76-2.74) | 1.45 (1.14-1.84) | 1.46 (1.15-1.85) | 1.43 (1.13-1.83) | 1.41 (1.11-1.80) | 1.40 (1.09-1.80) | |
| TC per 1-SD increment | 1.23 (1.11-1.36) | | | | | | |
| LDL-C per 1-SD increment | 1.02 (0.92-1.14) | | | | | | |
| HOMA-IR per 1-SD increment | 1.53 (1.31-1.78) | | | | 1.15 (0.96-1.39) | | |
| hsCRP ≥3.0 mg/L | 1.49 (1.02-2.16) | | | | | 1.44 (0.99-2.11) | |
| Current smoker | 0.99 (0.80-1.24) | | | | | | |
| Light drinker[f] | 1.03 (0.81-1.31) | | | | | | |
| MetS | 2.43 (1.81-3.26) | | | | | | 1.73 (1.27-2.35) |
| Incident hypertension | 1.85 (1.44-2.37) | | 1.73 (1.35-2.23) | 1.71 (1.33-2.20) | 1.71 (1.33-2.20) | 1.85 (1.42-2.40) | 1.70 (1.32-2.18) |
| Incident diabetes | 1.59 (0.87-2.92) | | | | | | |

Multivariate models are adjusted for all other variables listed for the model. Glomerular filtration rate 1 SD = 9.16 mL/min per 1.73 m$^2$, TC 1 SD = 34.3 mg/dL, LDL-C 1 SD = 29.4 mg/dL, HOMA-IR 1 SD = 1.48.

[a] BMI ≥25 kg/m$^2$.

[b] Fasting serum glucose ≥110 mg/dL.

[c] Blood pressure ≥130/85 mm Hg.

[d] HDL-C <40 mg/dL.

[e] TG ≥150 mg/dL.

[f] 10∼20 g of alcohol per day.

Table 4
Adjusted relative risk of incidence of CKD with the presence of NAFLD according to subgroups of MetS, insulin resistance, inflammation, and liver function test

| Subgroups | | Cases/person-years | ID[a] | Adjusted RR (95%, CI)[b] | *P* for interaction[b] |
|---|---|---|---|---|---|
| Without MetS | No NAFLD | 160/18218.7 | 8.78 | 1.00 | .647 |
| | NAFLD | 111/6553.6 | 16.94 | 1.59 (1.25-2.03) | |
| With MetS | No NAFLD | 9/602.2 | 14.95 | 1.00 | |
| | NAFLD | 44/1342.6 | 32.77 | 1.84 (0.89-3.78) | |
| HOMA-IR <4th Q[c] | No NAFLD | 138/15919.7 | 8.67 | 1.00 | .829 |
| | NAFLD | 75/4282.0 | 17.52 | 1.43 (1.07-1.92) | |
| HOMA-IR ≥4th Q[c] | No NAFLD | 31/2901.2 | 10.69 | 1.00 | |
| | NAFLD | 80/3614.2 | 22.13 | 1.59 (1.04-2.44) | |
| hsCRP <4th Q[c] | No NAFLD | 130/14273.6 | 9.11 | 1.00 | .152 |
| | NAFLD | 79/4981.4 | 15.86 | 1.27 (0.94-1.73) | |
| hsCRP ≥4th Q[c] | No NAFLD | 39/4547.3 | 8.58 | 1.00 | |
| | NAFLD | 76/2914.7 | 26.07 | 1.64 (1.04-2.58) | |
| ALT <4th Q[c] | No NAFLD | 153/16688.2 | 9.17 | 1.00 | .169 |
| | NAFLD | 72/3721.9 | 19.34 | 1.44 (1.07-1.93) | |
| ALT ≥4th Q[c] | No NAFLD | 16/2132.7 | 7.50 | 1.00 | |
| | NAFLD | 83/4174.3 | 20.01 | 2.20 (1.24-3.91) | |
| AST <4th Q[c] | No NAFLD | 149/16338.9 | 9.12 | 1.00 | .801 |
| | NAFLD | 91/4582.7 | 19.86 | 1.49 (1.12-1.97) | |
| AST ≥4th Q[c] | No NAFLD | 20/2482.0 | 8.06 | 1.00 | |
| | NAFLD | 64/3313.5 | 19.31 | 1.82 (1.12-2.96) | |
| GGT <4th Q[c] | No NAFLD | 140/15835.7 | 8.84 | 1.00 | .008 |
| | NAFLD | 61/4465.7 | 13.66 | 1.09 (0.79-1.50) | |
| GGT ≥4th Q[c] | No NAFLD | 29/2985.2 | 9.71 | 1.00 | |
| | NAFLD | 94/3430.5 | 27.40 | 2.31 (1.53-3.50) | |

ID indicates incidence density.
[a] Per 1000 person-years.
[b] Adjustment for age, baseline GFR, incident hypertension, TG (except for MetS), and HDL (except for MetS).
[c] 4th Q, 75 percentile: HOMA-IR 75 percentile = 2.12, hsCRP 75 percentile = 1.0 mg/L, ALT 75 percentile = 37 U/L, AST 75 percentile = 28 U/L, GGT 75 percentile = 36 U/L.

associated with the development of microalbuminuria [29]. In our own previous study, an elevated GGT level was shown to be an independent predictor for CKD [14]. Some studies have suggested that elevated GGT predicts cardiovascular disease and all-cause mortality [30,31]. Although the mechanisms that explain the contribution of GGT to adverse health outcome have not been fully elucidated, the association between GGT and CKD could be related to vascular and related disorders [32]. In this study, the relationship between NAFLD and CKD risk was more evident in the NAFLD group with elevated GGT compared with the NAFLD group without elevated GGT. Although its value in NAFLD patients has not yet been established, a previous study showed that elevated GGT was an indication of more severe NAFLD [33]. In addition to liver cells, GGT is also expressed by proximal convoluted tubules of the kidney [34]. Therefore, the increased GGT in this sample could be an indication either of a more severe NAFLD or of subclinical renal disease. Several studies found an independent association between GGT and the risk of type 2 diabetes mellitus [35,36]. Because the diagnosis of diabetes was only based on fasting blood glucose in our study, increased GGT may be related to unrecognized diabetes, which could be diagnosed by an oral glucose tolerance test. Therefore, establishing that NAFLD with elevated GGT is a risk factor for CKD will require additional mechanistic studies that further assess the origins of the increased GGT and evaluate NAFLD spectrum and insulin resistance.

The study had several limitations. First, NAFLD was not assessed by biopsy because it is invasive and impractical for routine clinical practice. Although the sensitivity and specificity for detecting >33% steatosis are between 67% and 89% and between 77% and 93%, respectively [37,38], an incorrect classification may arise in 10% to 30% of cases. In the present study, the diagnosis of NAFLD was based on the exclusion of the known etiologic factors responsible for liver disease and ultrasound examination results; but the diagnosis was not confirmed by liver biopsy. In addition, limitation of this study might include possible underestimation of alcohol intake because this was self-reported by the participants in the study.

Second, serum creatinine levels and calculated GFR were used to define CKD. Although inulin or iothalamate clearance technique might provide a more sensitive estimate of renal function, serum creatinine is widely used in large epidemiologic studies and in clinical practice for estimating renal function [39]. Therefore, our findings are applicable to clinical and public health practice settings. Ethnic factors that are characteristic for the Asian population are not well established with respect to using equations that estimate GFR [40].

Third, dipstick urinalysis has decreased sensitivity and specificity in the diagnosis of proteinuria. The National

Kidney Foundation Kidney Disease Outcome Quality Initiation Advisory Board recommended that under most circumstances, spot urine samples should be used to detect and monitor proteinuria in adults and that it was not usually necessary to obtain a timed urine collection (overnight or 24-hour) for these evaluations in adults [41]. In our study, although the variables measured as end points indicating CKD (estimated GFR and proteinuria) were subject to biological variation and analytic error, of which the magnitude may be difficult to estimate, the previously known risk factors for CKD such as obesity, MetS [9], hsCRP [28], and insulin resistance [11] were associated with incident CKD in age-adjusted analyses. Finally, although the potential selection bias was minimized by the selection of a work-center–based population who showed a high participation rate, the study participants were limited to middle-aged, healthy Korean men, therefore limiting the generalizability of the study findings to other populations.

In conclusion, in the present prospective study of nonhypertensive and nondiabetic Korean male workers, NAFLD with elevated GGT was independently associated with an increased risk for CKD development; and this association remained significant even after adjustment for insulin resistance assessed by HOMA-IR, MetS, and low-grade inflammation measured by hsCRP. Therefore, our study suggests that further investigation of NAFLD with elevated GGT will provide insights into the pathogenesis of CKD.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.metabol.2007.11.022.

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