

Table 1. Principal observational cohort studies examining the association between NAFLD and the risk of incident stage ≥ 3 CKD (ordered by publication year).

Authors, Year (Ref.)	Study Characteristics	Diagnosis of NAFLD	Diagnosis of CKD & Number of incident cases	Covariate Adjustments	Main Findings
Ryu S <i>et al.</i> 2007 (19)	Community-based cohort study: 10,337 nondiabetic and non-hypertensive South Korean male workers with normal kidney function and no overt proteinuria at baseline. Follow-up: 3 years	Liver enzymes (<i>i.e.</i> , serum GGT levels)	eGFR <60 mL/min/1.73 m ² and/or overt proteinuria (urinary dipstick ≥ 1); 366 patients developed incident CKD during follow-up	Age, BMI, alcohol intake, smoking, baseline eGFR, triglycerides, HDL-cholesterol, C-reactive protein, HOMA-insulin resistance, and incident cases of hypertension and diabetes	Elevated serum GGT levels (<i>i.e.</i> , top quartile) were independently associated with increased risk of incident CKD (aHR 1.87; 95% CI 1.31-2.67)
Chang Y <i>et al.</i> 2008 (20)	Community-based cohort study: 8,329 nondiabetic and non-hypertensive South Korean men with normal kidney function and no overt proteinuria at baseline. Follow-up: 3.2 years	Ultrasonography; the prevalence of NAFLD was 30.2%	eGFR <60 mL/min/1.73 m ² and/or overt proteinuria (urinary dipstick ≥ 1); 324 patients developed incident CKD during follow-up	Age, BMI, alcohol intake, hypertension, smoking, fasting glucose, baseline eGFR, triglycerides, HDL-cholesterol, LDL-cholesterol, HOMA-insulin resistance, C-reactive protein, incident cases of hypertension and diabetes	NAFLD was independently associated with increased risk of incident CKD (aHR 1.60; 95% CI 1.3-2.0)
Targher G <i>et al.</i> 2008 (21)	Prospective cohort study (Valpolicella Heart Diabetes Study): 1,760 Italian type 2 diabetic outpatients with preserved kidney function and no overt proteinuria, free of cardiovascular disease and known chronic liver diseases at baseline. Follow-up: 6.5 years	Ultrasonography; prevalence of NAFLD was 73.2%	eGFR <60 mL/min/1.73 m ² and/or overt proteinuria; 547 patients developed incident CKD during follow-up (428 developed decreased eGFR alone, 112 developed proteinuria, irrespective of eGFR, and 7 developed kidney failure; no patients developed nephrotic syndrome)	Age, sex, BMI, waist circumference, blood pressure, smoking, diabetes duration, hemoglobin A1c, triglycerides, HDL-cholesterol, LDL-cholesterol, baseline eGFR, use of antihypertensive, lipid-lowering, antiplatelet and hypoglycemic agents	NAFLD was independently associated with increased risk of incident CKD (aHR 1.49; 95% CI 1.1-2.2)
Arase Y <i>et al.</i> 2011 (22)	Retrospective cohort study: 5,561 Japanese middle-aged individuals with NAFLD and normal kidney function without overt proteinuria at baseline. Follow-up: 5.5 years	Ultrasonography and liver enzymes (<i>i.e.</i> , serum GGT levels). Prevalence of NAFLD was 100%	eGFR <60 mL/min/1.73 m ² and/or overt proteinuria (urinary dipstick ≥ 1); 263 patients developed incident CKD during follow-up	Age, sex, hypertension, diabetes, total cholesterol, triglycerides, HDL-cholesterol, serum liver enzymes, hemoglobin, white blood cells, platelets, baseline eGFR	Among patients with NAFLD, elevated serum GGT levels were independently associated with an increased risk of incident CKD (aHR 1.35; 95% CI 1.02-1.8)
Targher G <i>et al.</i> 2014 (23)	Prospective cohort study: 261 Italian type 1 diabetic adult outpatients with normal kidney function, free of cardiovascular disease and known chronic liver diseases	Ultrasonography; prevalence of NAFLD was 50.2%	eGFR <60 mL/min/ 1.73 m ² and/or overt proteinuria; 61 patients developed incident CKD during follow-up (28 developed decreased eGFR with abnormal albuminuria, 21	Age, sex, diabetes duration, hemoglobin A1c, hypertension, baseline eGFR, presence of microalbuminuria	NAFLD was independently associated with an increased risk of incident CKD (aHR 1.85; 95% CI 1.03-3.3). Measurement of NAFLD provided incremental risk

	at baseline. Follow-up: 5.2 years		developed reduced eGFR alone, and 12 developed macroalbuminuria alone; no patients developed kidney failure; no patients developed nephrotic syndrome)		reclassification beyond that of conventional CKD risk factors
Huh JH <i>et al.</i> 2017 (24)	Prospective cohort study: 4,761 South Korean adults with normal kidney function and no overt proteinuria and free of cardiovascular disease and known chronic liver diseases at baseline. Mean follow-up: 10 years	Fatty liver index (FLI); prevalence of NAFLD (defined as FLI ≥ 60) was 12.6%	eGFR < 60 mL/min/1.73 m ² ; 724 individuals developed incident CKD during follow-up	Age, sex, smoking, diabetes status, physical exercise, alcohol intake, protein intake, systolic blood pressure, total cholesterol, C-reactive protein, baseline eGFR	FLI ≥ 60 was independently associated with increased risk of incident CKD (aHR 1.46; 95% CI 1.19-1.79). FLI provided incremental risk reclassification beyond that of conventional CKD risk factors
Shen ZW <i>et al.</i> 2017 (25)	Prospective cohort study: 21,818 Chinese adults with normal kidney function and no overt proteinuria at baseline, who received routine health examination. Follow-up: 5 years	Liver enzymes (<i>i.e.</i> , serum GGT levels)	eGFR < 60 mL/min/1.73 m ² and/or overt proteinuria (urinary dipstick $\geq 1+$); 1,456 individuals developed incident CKD during follow-up	Age, sex, BMI, alcohol intake, serum creatinine, albumin, alanine aminotransferase, hemoglobin, white blood count, triglycerides, total cholesterol, hypertension, smoking, history of cardiovascular disease, history of diabetes	Elevated serum GGT levels (<i>i.e.</i> , top quartile) were independently associated with an increased risk of incident CKD (aHR 1.33, 95% CI 1.07-1.64)
Kunutsor SK <i>et al.</i> 2017 (26)	Prospective cohort study (Kuopio Ischemic Heart Disease Study): 2,338 Finnish middle-aged men with normal kidney function at baseline. Median follow-up: 25.6 years	Liver enzymes (serum GGT levels)	eGFR < 60 mL/min/1.73 m ² ; 221 individuals developed incident CKD during follow-up	Age, BMI, systolic blood pressure, history of hypertension, smoking, history of coronary heart disease, history of diabetes, total cholesterol, HDL-cholesterol, alcohol intake, baseline eGFR	Elevated serum GGT levels (<i>i.e.</i> , top quartile) were not independently associated with increased risk of incident CKD (aHR 0.97, 95% CI 0.64-1.47)
Sinn DH <i>et al.</i> 2017 (27)	Retrospective cohort study: 41,430 South Korean adults with normal kidney function and no overt proteinuria at baseline, free from known chronic liver diseases. Follow-up: 4.2 years	Ultrasonography; advanced NAFLD fibrosis assessed by the NFS (≥ -1.455), FIB4 score (≥ 1.45) or APRI index (≥ 0.5); prevalence of NAFLD was 34.3%	eGFR < 60 mL/min/1.73 m ² ; 691 participants developed incident CKD during follow-up	Age, sex, BMI, smoking, alcohol intake, systolic blood pressure, hemoglobin A1c, LDL-cholesterol, use of hypoglycemic and lipid-lowering medications, baseline eGFR, time-varying development of diabetes and hypertension over the follow-up	NAFLD was independently associated with increased risk of incident CKD (aHR 1.21, 95% CI 1.03-1.44). The association between NAFLD and CKD was consistent in all subgroups analyzed. In addition, advanced NAFLD fibrosis (as detected by a NFS ≥ -1.455) was associated with even a higher risk of incident

	CKD (aHR 1.59, 95%CI 1.31-1.93). When NAFLD participants were classified according to APRI index and FIB4 score, those with higher APRI index or FIB4 score also had an increasing risk of incident CKD
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Abbreviations: aHR, adjusted hazard ratio; AST, aspartate aminotransferase; APRI, AST to platelet ratio index; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FIB4, fibrosis-4 score; GGT, gamma-glutamyltransferase; HOMA, homeostasis model assessment; NFS, NAFLD fibrosis score.

Note: eGFR was estimated by using either the four-variable Modification of Diet in Renal Disease (MDRD) study equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equation (that was used by the last five studies reported in this table).