

ONLINE-ONLY SUPPLEMENTARY MATERIAL

Supplementary Table 1. Principal retrospective and prospective cohort studies that have examined the association between NAFLD/NASH and risk of all-cause or cause-specific mortality (ordered by study design and publication year).

Author, References	Study characteristics	NAFLD diagnosis	Study outcomes	Statistical adjustments	Main results
Matteoni et al. Gastroenterology 1999;116: 1413–1419	Retrospective cohort study: 132 patients with NAFLD and elevated serum liver enzymes. Mean follow-up: 18 years	Biopsy	All-cause and cause specific mortality	None	Patients with NASH had higher risk of all-cause and liver-related mortality when compared to those without. CVD mortality did not differ between the two groups
Jepsen et al. Hepatogastroenterology 2003;50:2133–2136.	Retrospective cohort study: 1,800 patients discharged with a hospital diagnosis of NAFLD. Mean follow-up: 6.8 years	Ultrasound	All-cause and cause specific mortality	Controls from the general population were matched to cases for age and sex	Patients with NAFLD had higher risk of all-cause, CVD and liver-related mortality when compared to matched population
Dam-Larsen et al. Gut 2004;53:750–755	Retrospective cohort study: 215 patients who had a liver biopsy performed during the period 1976–1987. Median follow-up: 16.7 years	Biopsy	All-cause and cause specific mortality	Controls from the general population were matched to cases for age and sex	No difference in all-cause and cause-specific mortality between NAFLD patients and matched population
Adams et al. Gastroenterology 2005; 129; 113–121	Retrospective community-based cohort study: 420 patients with NAFLD. Mean follow-up: 7.6 years	Imaging or Biopsy	All-cause and cause specific mortality	Controls from the general population were matched to cases for age and sex	Patients with NAFLD had higher risk of all-cause, CVD and liver-related mortality compared with matched population
Targher et al. Diabetes Care 2007;30: 2119-2121	Prospective cohort study: 2,103 individuals with T2DM without baseline viral hepatitis and CVD. Follow-up: 6.5 years	Ultrasound	CVD mortality and events	Age, sex, smoking, diabetes duration, HbA1c, LDL-cholesterol, medication use, MetS	NAFLD was associated with higher risk of fatal and non-fatal CVD events
Ong et al. J Hepatol. 2008;49:608-612	Population-based study: 12,822 individuals from the Third National Health and Nutrition Examination Survey (NHANES III). Median follow-up: 8.7 years	Ultrasound	All-cause and cause specific mortality	Age, sex, race, educational level, income, BMI, hypertension, diabetes, MetS	NAFLD was associated with higher risk of all-cause and liver-related mortality

Haring et al. Hepatology. 2009;50:1403-1411	Population-based study: 4,160 individuals from Study of Health in Pomerania (SHIP). Median follow-up: 7.3 years	Ultrasound and liver enzymes	All-cause mortality	Age, waist circumference, alcohol consumption, physical activity, educational level, civil status, income, functional comorbidity index	Elevated serum GGT levels were associated with higher risk of all-cause mortality in men, but not in women. This association was stronger in men with NAFLD on ultrasound
Rafiq et al. Clin Gastroenterol Hepatol. 2009;7:234-238	Retrospective cohort study: 173 patients with NAFLD and elevated serum liver enzymes. Mean follow-up: 13 years	Biopsy	All-cause and cause specific mortality	None	Most common causes of death were CVD, malignancy, and liver disease. All-cause mortality did not differ between patients with and without NASH. Liver-related mortality was higher in NASH patients
Adams et al. Am J Gastroenterol. 2010;105:1567-1573	Community-based cohort study: 337 patients with T2DM from Olmsted County. Mean follow-up: 10.9 years	Imaging or biopsy	All-cause and cause specific mortality	Age, sex, date of diabetes diagnosis, obesity	NAFLD was associated with higher risk of all-cause mortality, but not with higher risk of CVD and cancer-related mortality
Söderberg et al. Hepatology 2010;51:595–602	Retrospective cohort study: 118 patients with NAFLD and raised serum liver enzymes. Mean follow-up: 24 years	Biopsy	All-cause and cause specific mortality	Controls were matched to cases for age, sex and calendar period	Patients with NASH, but not those with simple steatosis, had higher risk of all-cause, CVD and liver-related mortality compared to matched general population
Bhala et al. Hepatology. 2011;54:1208-1216	Retrospective international cohort study: 247 patients with NAFLD with advanced fibrosis or cirrhosis and 264 patients with HCV infection who were naïve or non-responders to treatment. Mean follow-up: 85.6 months for NAFLD cohort and 74.9 months for the HCV cohort	Biopsy	All-cause mortality as well as liver and non-liver complications	Age, sex, BMI, presence of diabetes and dyslipidemia	Patients with NAFLD with advanced fibrosis or cirrhosis had lower risk of liver-related complications than corresponding patients with HCV infection, but similar all-cause mortality and CVD events
Lazo et al. BMJ. 2011;343:d6891	Population-based study: 11,371 adults from the Third National	Ultrasound	All-cause and cause specific mortality	Sex, alcohol consumption, BMI, diabetes, education,	NAFLD was not independently associated with higher risk of

	Health and Nutrition Examination Survey, with the assessment of hepatic steatosis. Mean follow-up: 14.5 years			dyslipidemia, hypertension, physical activity, race, smoking	mortality from all-causes, CVD, cancer or liver disease
Stepanova et al. Clin Gastroenterol Hepatol. 2012;10:646-650	Population-based study: 14,105 patients from the Third National Health and Nutrition Examination Survey, conducted from 1988 to 1999, with the assessment of hepatic steatosis. Mean follow up: 14.3 years	Ultrasound	Cause specific mortality	Age, sex, diabetes, family history of myocardial infarction, obesity, race, smoking	NAFLD was not associated with higher risk of CVD mortality
Younossi et al. Metabolism. 2013;62:352-360	Population-based study: 1,448 patients from the Third National Health and Nutrition Examination Survey (conducted from 1988 to 1994). Follow-up: 15 years	Ultrasound	All-cause and cause specific mortality	Age, race, smoking, diabetes	NAFLD patients with MetS had higher risk of all-cause, liver-related and CVD mortality
Treepasertsuk et al. World J Gastroenterol. 2013;19:1219-1229	Longitudinal study: 302 patients with NAFLD. Mean follow up: 12 years	H-ICDA code and NAFLD fibrosis score (NFS)	All-cause mortality	Presence of CVD, medication use	A higher NFS at baseline was associated with increased risk of all-cause mortality
Kim et al. Hepatology. 2013;57:1357-1365	Population-based study: 11,154 from National Health and Nutrition Examination Survey conducted in 1988-1994. Mean follow-up: 15 years	Ultrasound and NFS	All-cause and cause specific mortality	Age, sex, race, ethnicity, education, income, diabetes, hypertension, history of CVD, medications, smoking, waist circumference, alcohol and caffeine consumption, lipids, transferrin saturation, CRP	NAFLD was not associated with increased risk of all-cause mortality. However, advanced fibrosis (as detected by NFS) was an independent predictor of increased mortality, mainly from CVD
Stepanova et al. Dig Dis Sci. 2013;58:3017-3023	Retrospective cohort study: 289 patients with biopsy-proven NAFLD. Median follow-up: 12.5 years	Biopsy	All-cause and cause specific mortality	Age, sex, race, obesity, diabetes, dyslipidemia	NASH patients had higher risk of liver-related mortality than those without NASH. Additionally, patients with NAFLD and T2DM were at highest risk for all-cause

					and liver-related mortality
Xun et al. Clin Exp Pharmacol Physiol. 2014;41:643-649	Longitudinal study: 180 patients with NAFLD. Median follow-up: 6.6 years	Ultrasound and NFS	All-cause mortality	Age, sex, diabetes, blood pressure, serum GGT, uric acid	NAFLD patients with advanced fibrosis (as detected by NFS) had higher risk of all-cause mortality
Angulo et al. Gastroenterology. 2015;149:389-397	Retrospective cohort study: 619 patients with biopsy-proven NAFLD. Median follow-up 12.6 years	Biopsy	All-cause mortality	Age, sex, race, BMI, diabetes, hypertension, statin use, site, smoking, calendar year of liver biopsy, biopsy size	Liver fibrosis stage, but not other histologic NASH features, were associated with all-cause mortality, liver transplantation, and liver-related events
Ekstedt et al. Hepatology. 2015;61:1547-1554	Retrospective cohort study: 229 patients with biopsy-proven NAFLD Mean follow-up: 26.4 years	Biopsy	All-cause and cause specific mortality	Controls were matched to cases for age and sex	NAFLD patients had higher risk of all-cause, CVD and liver-related mortality compared with matched population. Stage of fibrosis, rather than presence of NASH, predicted all-cause and cause specific mortality
Zeb et al. J Am Coll Cardiol 2016;67:1965–1966	Population-based study: 6,814 participants from the MESA study (Multi-Ethnic Study of Atherosclerosis), who were free of clinical CVD at baseline. Median follow-up: 7.6 years	Computed tomography	All-cause mortality and CVD	Age, sex, ethnicity, study sites, diabetes, hypertension, BMI, lipids, smoking, family history of CVD, medications, CRP, coronary artery calcium	NAFLD was independently associated with higher risk of all-cause mortality and nonfatal CVD events
Unalp-Arida et al. Hepatology. 2016;63:1170-1183	Population-based study: 14,527 adult participants from National Health and Nutrition Examination Survey (NHANES), 1988-1994, who were negative for viral hepatitis B and C and iron overload. Follow-up: up to 23 years	Ultrasound and liver enzymes	All-cause and cause specific mortality	Age, sex, race, education, alcohol intake, smoking, caffeine intake, physical activity, BMI, waist-to-hip circumference ratio, diabetes, total and HDL cholesterol, blood pressure, CRP, kidney function	Severe hepatic steatosis and liver enzyme elevation were associated with higher liver-related mortality, but not with mortality from all-causes, CVD, cancer, or diabetes
Goossens et al. Clin Gastroenterol Hepatol. 2016;14:1619–1628	Retrospective cohort study: 492 individuals who underwent gastric bypass bariatric surgery. Median	Biopsy	All-cause mortality	Age, sex, BMI, hypertension	Patients with NASH had higher risk of all-cause mortality compared to

	follow-up: 10.2 years				those without NASH
Le et al. PLoS One. 2017;12: e0173499	Population-based study: 5,086 participants from the U.S. National Health and Nutrition Examination Survey, 1999–2012. Mean follow-up: 6.6 years	US-FLI >30 and NFS	All-cause mortality	Age, sex, race, BMI, diabetes, education, MetS, smoking	NAFLD patients with advanced fibrosis (detected by NFS) had higher risk of all-cause mortality
Keskin et al. Am J Cardiol. 2017;120:1720-1726	Longitudinal study: 360 patients with ST-segment elevation myocardial infarction. Mean follow-up: 2.6 years	Ultrasound	All-cause mortality	Age, sex, BMI, waist circumference, CRP, serum creatinine, diabetes, heart rate, hematocrit, hypertension, lymphocyte, medications, neutrophil, platelet count, SYNTAX score, troponin I, white blood cells	NAFLD was associated with higher risk of all-cause mortality
Mahady et al. J Clin Gastroenterol. 2017;51:439-445	Longitudinal study: 2,061 elderly patients with linkage to a National Death Registry. Median follow up: 10 years	Liver enzymes	All-cause and cause specific mortality	Age, sex, smoking, alcohol intake	Patients with elevated serum liver enzymes had higher risk of all-cause and CVD mortality
Wild et al. Diabetes Care. 2018;41:341-347	Retrospective cohort study: 134,368 patients with T2DM (1,452 with NAFLD) who had one or more hospital admission records. Mean follow-up: 4.3 years for CVD and 4.7 years for mortality	ICD-9/ICD-10 codes	All-cause and cause specific mortality	Age, sex, socioeconomic status, smoking, hypertension, lipids, HbA1c, medications, family CVD history	Patients with NAFLD had higher risk of all-cause and cause-specific mortality compared to the group with no records of liver disease
Valbusa et al. Int J Cardiol 2018;265:162-168	Longitudinal study: 264 elderly patients consecutively admitted for acute heart failure to the hospital. Mean follow-up: 1.9 years	Ultrasound	All-cause mortality	Age, sex, body weight, history of heart failure, diabetes, chronic heart disease, CKD, COPD, presence of pacemakers or implantable defibrillators, hospital ward, blood pressure, LV-ejection fraction, medications, plasma NT-	NAFLD was associated with higher risk of all-cause mortality

				proBNP, albumin, GGT levels	
Unalp-Arida et al. Aliment Pharmacol Ther. 2018;48:1003-1016	Population-based study: 9,200 viral hepatitis-negative adults from the third National Health and Nutrition Examination Survey, 1988-1994. Mean follow-up 23.3 years	US-FLI, NAFLD-liver fat score (NAFLD LFS), and hepatic steatosis index	All-cause and cause-specific mortality	Age, sex, race, education, alcohol use, smoking, caffeine intake, physical activity, BMI, waist/hip circumference ratio, diabetes, lipids, CRP, hypertension	A higher US-FLI and NAFLD-LFS were associated with higher risk of liver-related mortality
Hwang et al. Clin Gastroenterol Hepatol. 2018;16:1131-1137	Population-based study: 318,224 individuals from the Kangbuk Samsung Health Study cohort. Median follow-up: 5.7 years	Ultrasound	All-cause and cause specific mortality	Age, BMI, smoking, alcohol consumption, physical activity	NAFLD was associated with higher risk of all-cause death and death from cancer, CVD, and liver disease only in women, but not in men
Allen et al. Hepatology. 2018;67:1726-1736	Community-based study: 3,869 NAFLD patients and 15,209 controls. Median follow-up: 7 years	ICD-9 codes	All-cause mortality	Age, sex, BMI, hypertension, diabetes, dyslipidemia	NAFLD was associated with higher risk of all-cause mortality
Caruso et al. BMJ Open 2019;9:e027379	Community-based study: 1,445 older patients from the Multicentrica Colelitiasi III. Median follow-up: 12 years	Ultrasound	All-cause and specific-cause mortality	Age, sex, , waist circumference smoking, diabetes, blood pressure, myocardial infarction	Severity of steatosis was not independently associated with higher risk of all-cause mortality in NAFLD patients
Chinnadurai et al. Nephrol Dial Transplant. 2019;34:449-457	Longitudinal study: 1,148 CKD patients who had undergone ultrasound imaging for clinical reasons. Median follow-up: 5.4 years	Ultrasound	All-cause and cause specific mortality	Age, sex, BMI, hypertension, dyslipidemia, diabetes, eGFR, ischemic heart disease, heart failure, blood pressure, medications, smoking	NAFLD was associated with higher risk of CVD mortality but not with all-cause mortality
Önnerhag et al. Clin Res Hepatol Gastroenterol. 2019;43:542-550	Longitudinal study: 120 patients with biopsy-proven NAFLD compared with 1,755 individuals from the population-based prospective cohort Malmö Preventive Project. Mean Follow-up: 19.5 years	Biopsy	All-cause mortality	Age, sex, diabetes, hypertension	NAFLD patients with CKD had higher risk of all-cause mortality compared to those with NAFLD and no-CKD
Golabi et al. BMC Gastroenterology 2019;19:56	Population-based study: 3,271 patients from Third National Health and Nutrition Examination Survey.	US-FLI > 30	All-cause and cause specific mortality	Sex, smoking, hypertension, dyslipidemia, history of cancer, history of CVD	NAFLD was associated with higher rates of all-cause and CVD mortality for 60-74-year-old individuals, but

	Median follow-up: 12.3 years				not for those older than 74 years
Olubamwo et al. BMJ Open Gastroenterol. 2019;6:e000219	Prospective cohort study: 1,893 men from the Kuopio Ischemic Heart Disease Risk Factor Study. Mean follow-up: 20 years	FLI >30	All-cause and specific-cause mortality	Age, family history of diabetes, family history of CVD, smoking, alcohol consumption, physical activity, fruit/berry consumption, CRP, fibrinogen, leucocytes, thrombocytes, blood pressure, insulin, fasting glucose, lipids	Patients with FLI ≥60, when compared to those with FLI <30, had higher rates of all-cause, CVD; non-CVD and cancer- related mortality
Alvarez et al. Hepatology. 2019 Nov 16. doi: 10.1002/hep.31040. [Epub ahead of print]	Population-based study: 12,253 adult individuals with ultrasound assessment from the Third National Health and Nutrition Examination Survey and mortality follow-up through 2015. Median follow-up: 23.3 years	Ultrasound	All-cause and cause-specific mortality	Age, gender, BMI, race, education, physical activity, smoking, alcohol intake	NAFLD was associated with higher all-cause mortality. Overall population attributable fraction for all- cause mortality associated with NAFLD was 7.5% (95% CI 3-12)

NB: The cohort studies we included in the table were searched on PubMed database but we did not perform a formal systematic review for the selection of these studies.

Abbreviations: ALD, alcoholic liver disease; ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; GGT, gamma glutamyltransferase; H-ICDA, hospital international classification of diseases adapted; ICD, international classification of diseases; HR, hazard ratio; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; US-FLI, United States fatty liver index; NFS, NAFLD fibrosis score.

Supplementary Table 2. Principal retrospective and prospective cohort studies investigating the association between NAFLD and risk of developing extra-hepatic cancers (ordered by publication years).

Authors, Ref	Study characteristics	NAFLD diagnosis	Statistical adjustments	Main results
Lee et al. J Gastroenterol Hepatol 2012;27:91-95	Retrospective cohort study: 5,517 women undergoing screening colonoscopy. Mean follow-up: 4.5 years	Ultrasound	Age, BMI, smoking, hypertension, dyslipidemia, fasting glucose	NAFLD was independently associated with increased risk of incident colorectal adenomas and cancer
Arase <i>et al.</i> Hepatol. Res. 2012;42:264-272	Longitudinal studies: 1,600 patients with NAFLD and 1,600 patients with hepatitis C virus matched for age, sex. Mean follow-up: 8.2 years	Ultrasound	Age, smoking, diabetes	Cumulative rate of carcinogenesis was 13.9% in the NAFLD group and 28.2% in the HCV group (p<0.05). The most frequent malignancies in the NAFLD group were gastric, colon and prostate cancers
Huang et al. Colorectal Dis 2013;15:830-835	Retrospective cohort study: 1,522 individuals undergoing two consecutive colonoscopies at Taipei General Hospital. Mean follow-up: 2.6 years	Ultrasound	Age, sex, BMI, smoking, hypertension, diabetes, Mets	NAFLD was independently associated with increased risk of incident colorectal adenomas
Choi <i>et al.</i> Endocr. Relat. Cancer 2014 ;21:343-353	Longitudinal studies: 293 consecutive prostate cancer patients who underwent radical prostatectomy were enrolled from two hospitals in Korea and randomly assigned to training (n=147) or validation set (n=146). Mean follow-up: 4.2 years	Ultrasound or computed tomography	Pathological Gleason score, pathological stage, positive surgical margin, positive lymphnodes	NAFLD was associated with <i>decreased</i> prostate cancer biochemical recurrence after radical prostatectomy for prostate cancer
Yang et al. PLoS One 2017;12:e0182014	Retrospective cohort study: 1,023 individuals undergoing screening colonoscopy. Mean follow-up: 5 years	Ultrasound or computed tomography	Age, sex, smoking, hypertension, diabetes, medications	NAFLD was independently associated with increased risk of colorectal tumors
Kim et al. J Hepatol. 2018;68:140-146	Retrospective cohort study: 25,947 individuals who were followed up for at least 1 year after having a health checkup at a tertiary hospital in Korea	Ultrasound and NFS or FIB-4 scores	Age, sex, smoking, diabetes, hypertension, GGT, plasma lipids	NAFLD was independently associated with increased risk of colorectal cancer in men and increased risk of breast cancer in women. NAFLD was also independently associated with increased risk of HCC. A high NFS (or a high FIB-4 score) showed a strong association with cancer development

Choi et al. PLoS One. 2018;13:e0201308	Population-based study: 10,516,985 Korean men. Median follow up: 5 years	FLI or hepatic steatosis index	Age, smoking, alcohol consumption, regular physical activity, yearly income, diabetes, hypertension, dyslipidemia	NAFLD was associated with an increased risk of prostate cancer, especially in the elderly
Hamaguchi et al. BMJ Open Gastroenterol. 2019;6:e000295	Population-based study: 27,944 individuals who performed liver ultrasonography. Mean follow-up: 6.4 years	Ultrasound	Age, sex, smoking, alcohol consumption, physical activity	NAFLD patients with obesity had higher risk of incident gastric cancer and colorectal cancer than nonobese individuals without NAFLD
Allen et al. J Hepatology 2019;71:1229-1236	Community-based study: 4,722 individuals with NAFLD and 14,441 age- and sex-matched individuals without NAFLD. Median follow-up: 8 years	Hospital International Classification of Diseases Adapted (HICDA) codes	Controls were matched to cases by age and sex	NAFLD was associated with higher risk of cancers (mainly of gastrointestinal tract and uterus)
Lee et al. Medicine (Baltimore). 2019;98:e17277	Retrospective cohort study: 123 patients with breast cancer and 123 controls after propensity score matching. Follow-up: 12 years	Computed tomography	Diabetes, hemoglobin, platelet, alkaline phosphatase, albumin, CA 15-3, cancer stage, use of endocrine therapy	In patients with breast cancer, NAFLD was associated with tumor recurrence after curative surgery

Abbreviations: BMI, body mass index; FLI, fatty liver index; GGT, gamma-glutamyltransferase; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score