Nonalcoholic fatty liver disease and mortality from all causes, cardiovascular disease, and cancer: a meta-analysis

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Table S1. Search Strategy for PubMed and Embase databases

Table S1. Search strategy for PubMed database (from its inception to October 17, 2018)

No.	Search strategy	Items found
#1	(((Non-alcoholic Fatty Liver Disease[MeSH Terms]) OR "fatty liver"[Title/Abstract]) OR steatohepatitis[Title/Abstract]) OR steatosis[Title/Abstract]	37313
#2	((((((death[MeSH Terms]) OR mortality[MeSH Terms]) OR death*[Title/Abstract]) OR mortalit*[Title/Abstract]) OR surviv*[Title/Abstract]) OR fatalit*[Title/Abstract]	2212493
#3	(review[Publication Type]) OR Published Erratum[Publication Type]) OR Editorial[Publication Type]	2941870
#4	#1 AND #2	4270
#5	#4 NOT #3	2924

Table S1-2. Search strategy for Embase database (from its inception to October 18, 2018)

No.	Search strategy	Items found
#1	'nonalcoholic fatty liver'/exp OR 'fatty liver':ab,ti OR 'steatohepatitis':ab,ti OR 'steatosis':ab,ti	63002
#2	'death'/exp OR 'mortality'/exp OR 'death*':ab,ti OR 'mortalit*':ab,ti OR 'surviv*':ab,ti OR 'fatalit*':ab,ti	3269906
#3	'review':it OR 'erratum':it OR 'editorial':it	3149973
#4	#1 AND #2	8921
#5	#4 NOT #3.	7172

Table S2. Excluded studies after reading the full text and corresponding reasons for exclusion.

Author	Year	Study description	Reasons for exclusion
Unalp-Arida et al. [1]	2018	This prospective study utilized NHANES III data, and investigated the association between liver fat scores and mortality. The authors explored the association between NAFLD liver fat score and mortality, but the reference group was patients with low NAFLD liver fat score rather than those without NAFLD.	NAFLD patients as the reference group.
Pais et al. [2]	2018	A prospective study on the association of hepatic steatosis with the risk of atherosclerosis.	Data on outcomes of interest were not available.
Chen et al. [3]	2018	This study recruited a total of 764 colorectal cancer patients undergoing primary surgical resection, and investigated the association between NAFLD and colorectal cancer mortality.	NAFLD and colorectal cancer mortality.
Yu et al. [4]	2017	A large cohort study investigated the effect of the number of metabolic	Data on outcomes of interest were

		risk factors on the risk of liver-related death. No risk estimates of NAFLD and mortality were found.	not available.
Brown et al. [5]	2017	This prospective study utilized NHANES III data, and investigated the association between NAFLD and mortality among cancer survivors.	Duplicate report of included cohort.
Zeb et al. [6]	2016	This prospective study investigated the association between NAFLD and incident cardiac event. The authors found that NAFLD was significantly associated with a composite endpoint inclusive of all-cause death and non-fatal CVD events.	Data on outcomes of interest were not available.
Unalp-Arida et al. [7]	2016	This prospective study utilized NHANES III data, and investigated the association between hepatic steatosis and mortality in the U.S. population.	Fatty liver and mortality.
Perera et al. [8]	2016	This descriptive study included a total of 120 patients with acute coronary syndrome, and investigated the association between NAFLD	NAFLD and mortality from acute coronary syndrome.

and mortality from acute coronary syndrome.

Seko et al. [9]	2015	This retrospective cohort study investigated the predictors of overall mortality in patients with NAFLD.	Data on outcomes of interest were not available.
Onat et al. [10]	2015	This prospective study employed fatty liver index to define fatty liver, and investigated the association between fatty liver and mortality.	Fatty liver index and mortality.
Zoppini et al. [11]	2014	This study investigated the association between chronic liver disease and mortality. However, it only provided risk estimates associated with non-virus, non-alcohol-related chronic liver disease rather than NAFLD.	Data on outcomes of interest were not available.
Pisto et al. [12]	2014	This population-based cohort study investigated the association between fatty liver and mortality.	Fatty liver and mortality.
Haflidadottir et al. [13]	2014	This retrospective study showed that patients with alcoholic fatty liver had higher liver-related mortality than those with NAFLD.	Data on outcomes of interest were not available.
Cheung et al. [14]	2014	This prospective study utilized NHANES III data, and investigated the	NAFLD patients as the reference

association between NAFLD liver fat score and mortality. Moreover, the   group.

reference group was those with high NAFLD liver fat score.

Otgonsuren et al. [15]	2013	This study utilized NHANES III data, and only provided risk estimates of NAFLD and liver-specific mortality.	Duplicate report of included cohort.
Lerchbaum et al. [16]	2013	This prospective cohort study included a total of 3270 patients referred to coronary angiography, and investigated the association between fatty liver index and mortality.	Fatty liver index and mortality.
Kim et al. [17]	2013	This prospective study utilized NHANES III data, and investigated the association between NAFLD and mortality. Its median follow-up duration was same as the study by Lazo et al. (2010) (14.5y), but its sample size (11154) was less than the study by Lazo et al. (2010) (11371).	Duplicate report of included cohort.
Zhou et al. [18]	2012	This prospective cohort study investigated the natural course of NAFLD	Data on outcomes of interest were

		in a Chinese population, and showed that patients with NAFLD had higher mortality rates than those without. However, this study did not provide specific risk estimates on NAFLD and mortality.	not available.
Calori et al. [19]	2011	This population-based study investigated the association between fatty liver index and mortality in the general population.	Fatty live index and mortality.
Soderberg et al. [20]	2010	This study showed that subjects with NAFLD had an increased risk of death compared with the general population. However, patients in this study were included in a recent study by Ekstedt et al. (2015).	Duplicate report of included cohort.
Yun et al. [21]	2009	This prospective study investigated the association between alanine aminotransferase levels and mortality from cardiovascular disease or diabetes in a Korean population.	Data on outcomes of interest were not available.
Ong et al. [22]	2008	This prospective study utilized NHANES III data, and investigated the association between NAFLD and mortality. Of note, both sample size	Duplicate report of included cohort.

(11285) and follow-up duration (8.7y) of this study were less than the

study by Lazo et al. (2010).

Dunn et al. [23]	2008	This prospective study utilized NHANES III data, and investigated the association between NAFLD and mortality. Of note, both sample size (7574) and follow-up duration (8.7y) of this study were less than the study by Lazo et al. (2010).	Duplicate report of included cohort.
Targher et al. [24]	2007	This prospective study investigated the association between NAFLD diagnosed by ultrasound and incident cardiovascular disease events. In this study, cardiovascular disease events were defined as myocardial infarction, ischemic stroke, coronary revascularization, or cardiovascular death.	Data on outcomes of interest were not available.
Ekstedt et al. [25]	2006	This study showed that patients with NAFLD did not have an increased mortality compared with the general population. However, patients in	Duplicate report of included cohort.

		this study were included in a recent study by Ekstedt et al. (2015).	
Targher et al. [26]	2005	This prospective nested case-control study investigated the association between NAFLD and cardiovascular disease events. However, it did not report risk estimates of mortality from cardiovascular disease.	Data on outcomes of interest were not available.
Jepsen et al. [27]	2003	This retrospective cohort study provided standardized mortality ratio for patients with non-alcoholic or unspecified fatty liver, but it did not provide risk estimates for those with NAFLD separately.	Data on outcomes of interest were not available.
Matteoni et al. [28]	1999	This study compared clinical characteristics and outcomes of patients with different types of NAFLD. The reference group was patients with NAFLD.	NAFLD patients as the reference group.

Abbreviations: NHANES III, the third National Health and Nutrition Examination Survey; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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Table S3. Characteristics of included studies on NAFLD and mortality

Source; study location	Study population	Mean age (y)	Mean follow-up duration (y)	NAFLD cases/ sample size	Deaths	NAFLD diagnosis	Outcome assessment	Adjustment factors
Wild et al. (2018) [6]; UK	Population with type 2 diabetes	62.6	4.7	1452/ 132661	All-cause: 16424 CVD: 4469 cancer: 5673	Abdominal imaging or liver biopsy	National mortality records	Age, sex, antihypertensive treatment, cholesterol level, CVD history, glycated hemoglobin, hypertension, lipid-lowering treatment, smoking, and socioeconomic status
Valbusa et al. (2018) [26]; Italy	Population with acute heart failure	83.3	1.9	153/264	All-cause: 116	Ultrasonography	Contacting patients, family members, or patients' physician	Age, sex, body weight, chronic kidney disease, chronic obstructive pulmonary disease, coronary heart disease, diabetes, furosemide doses, γ- glutamyltransferase, history of heart failure, hospital ward, left ventricular ejection fraction, NT pro-brain natriuretic peptide, plasma albumin, systolic blood pressure, and use of

								antihypertensive drugs
Hwang et al. (2018) [14]; South Korea	General population	39.3	5.7 [1]	82899/ 318224	All-cause: 1613 CVD: 242 cancer: 748	Ultrasonography	Death certificate	Age, alcohol consumption, BMI, smoking, and physical activity (plus diabetes, hypertension, and hypercholesterolemia for CVD mortality only)
Chinnadurai et al. (2018) [10]; UK	Population with chronic kidney disease	66.0 [a]	5.4 [1]	183/852	All-cause: 271	Ultrasonography	Electronic patient records and National Statistic Office	Age, sex, BMI, cerebrovascular accidents, congestive cardiac failure, diabetes, diastolic blood pressure, estimated glomerular filtration rate, hyperlipidemia, hypertension, ischemic heart disease, malignancy, myocardial infarction, peripheral vascular disease, smoking, and systolic blood pressure
Allen et al. (2018) [7]; USA	General population	53.0 [a]	7.0 [1]	3869/19078	All-cause: 1551	Abdominal imaging or liver biopsy	Death certificate	(None, controls were matched to cases for age and sex)
Le et al. (2017) [11]; USA	General population	49.2	6.6	1936/6000	All-cause: 405	Ultrasonography	Death certificate	Age, sex, BMI, diabetes, education, metabolic syndrome, race, and

								smoking
Keskin et al. (2017)[22]; Turkey	Population with myocardial infarction	59.0	2.6	191/360	All-cause: 29	Ultrasonography	National Death Declaration system or follow-up interview	Age, sex, blood urea nitrogen, BMI, chronic kidney disease, C-reactive protein, creatine kinase, creatinine, diabetes, heart rate, hematocrit, hypertension, lymphocyte, medications, neutrophil, platelet count, SYNTAX score, systolic blood pressure, troponin I, waist circumference, and white blood cells
Ekstedt et al. (2015)[8]; Sweden	General population	48.8	26.4	229/2519	All-cause: 882 CVD: NA cancer: NA	Liver biopsy	Death registry	(None, controls were matched to cases for age and sex)
Mahady et al. (2014)[27]; Australia	General population	70.0	11.0	NA/2335	All-cause: 701 CVD: 203	Ultrasonography	National Death Index	Age, sex, and alcohol consumption
Stepanova et al. (2012)[12]; USA	General population	(20.0-74.0)	14.3	2492/11613	CVD: 591	Ultrasonography	Death certificate	Age, sex, diabetes, family history of myocardial infarction, obesity, race, and smoking
Lazo et al. (2011)[13];	General population	42.7	14.5 [1]	2515/11371	All-cause: 1836 CVD: 716	Ultrasonography	Death certificate	Sex, alcohol consumption, BMI, diabetes, education,

USA					cancer: 480			hypercholesterolemia, hypertension, physical activity, race, and smoking
Adams et al. (2010) [25]; USA	Population with type 2 diabetes	58.0	10.9	116/337	All-cause: 99 CVD: 36 cancer: 23	Abdominal imaging or liver biopsy	Death certificate	Age, sex, date of diabetes diagnosis, and obesity
Haring et al. (2009) [21]; Germany	General population	49.6	7.3 [a]	1249/4160	All-cause: 307 CVD: NA	Ultrasonography	Death certificate	Age, alcohol consumption, civil status, education, equalized income, functional comorbidity index, physical activity, and waist circumference
Adams et al. (2005) [9]; USA	General population	49.0	7.6	435/435	All-cause: 53	Abdominal imaging or liver biopsy	Death certificate	(None, controls were matched to cases for age and sex)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; NA, not available; NAFLD, nonalcoholic fatty liver disease.

[1] Median value.

Table S4 The results of quality assessment of included studies

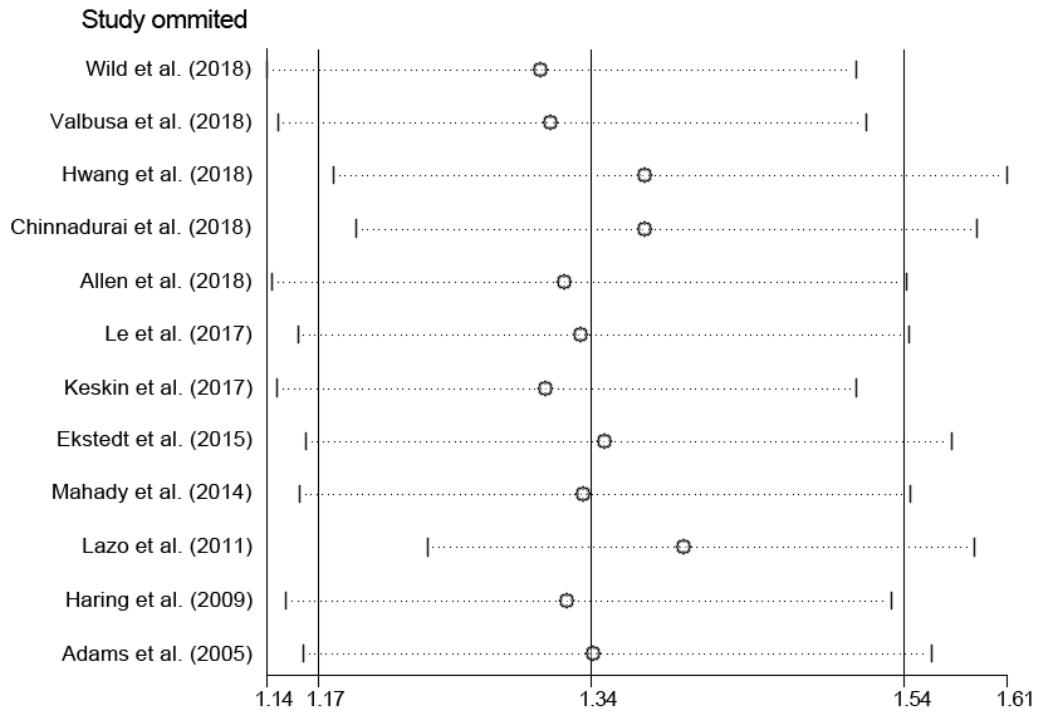| Study	Selection				Comparability		Outcome			Total Score
	Representativeness of exposed cohort ☆	Selection of non-exposed cohort ☆	Exposure ascertainment ☆	No history of disease ☆	Comparable on confounders ☆☆		Outcome Assessment ☆	Adequate follow-up (≥10y) ☆	Loss to follow-up rate (≤20%) ☆	
Wild et al. (2018) [6]		☆	☆		☆	☆	☆		☆	6
Valbusa et al. (2018) [26]		☆	☆		☆	☆			☆	5
Hwang et al. (2018) [14]	☆	☆	☆	☆	☆	☆	☆		☆	8
Chinnadurai et al. (2018) [10]		☆	☆		☆	☆	☆			5
Allen et al. (2018) [7]	☆	☆	☆	☆			☆		☆	6
Le et al. (2017) [11]	☆	☆	☆	☆	☆	☆	☆		☆	8
Keskin et al. (2017) [22]		☆	☆		☆	☆			☆	5
Ekstedt et al. (2015) [8]		☆	☆	☆			☆	☆	☆	6
Mahady et al. (2014) [27]	☆	☆	☆	☆	☆		☆	☆		7
Stepanova et al. (2012) [12]	☆	☆	☆	☆	☆	☆	☆	☆		8
Lazo et al. (2011) [13]	☆	☆	☆	☆	☆		☆	☆		7
Adams et al. (2010) [25]		☆	☆	☆	☆		☆	☆	☆	7
Haring et al. (2009) [21]	☆	☆	☆	☆	☆	☆	☆		☆	8
Adams et al. (2005) [9]		☆	☆	☆			☆		☆	5

Figure S1. Sensitivity analysis on NAFLD and all-cause mortality: the exclusion of a single study in turn. The study cited on the left is the one left out in each turn. The circle represents the summary risk estimates after exclusion of a single study, and the corresponding dot line represents 95% confidence interval. The middle vertical solid line represents summary risk estimates of all included studies, and left and right vertical solid line represent lower limit and upper limit, respectively
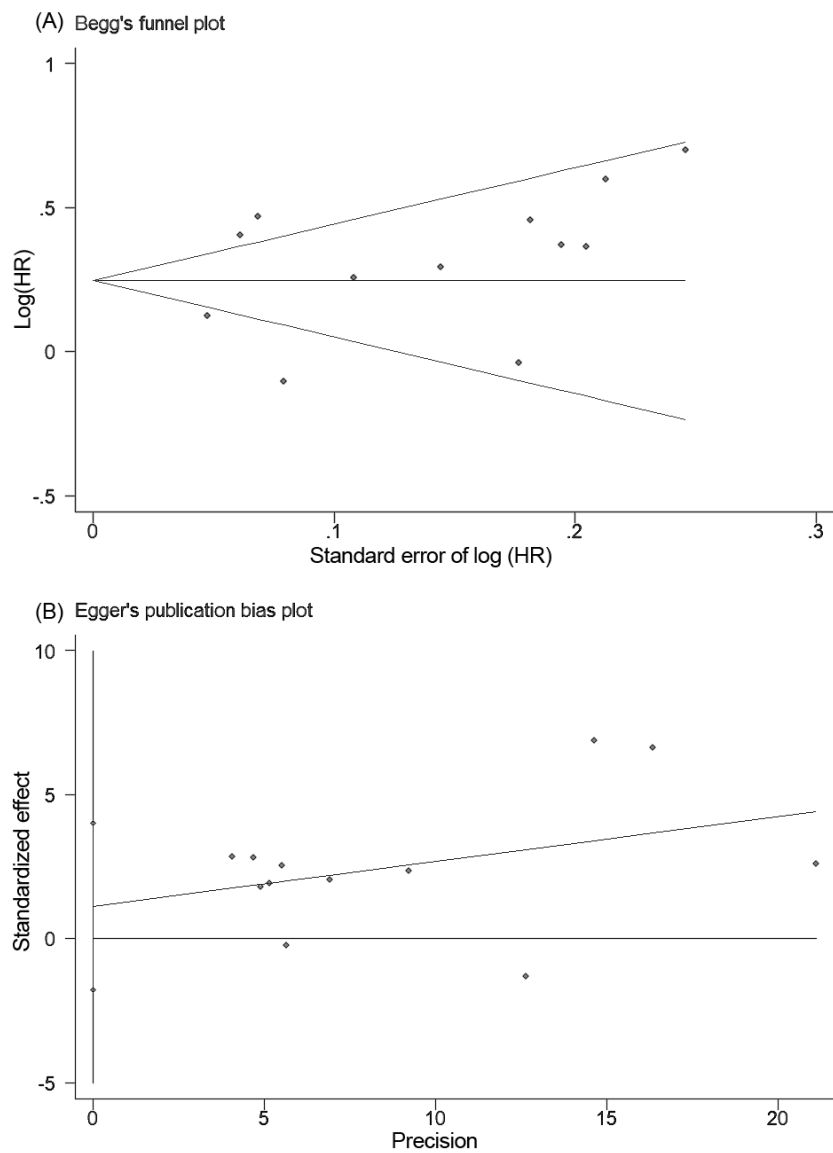
Figure S2. Results of Begg's test and Egger's test on the association of NAFLD with
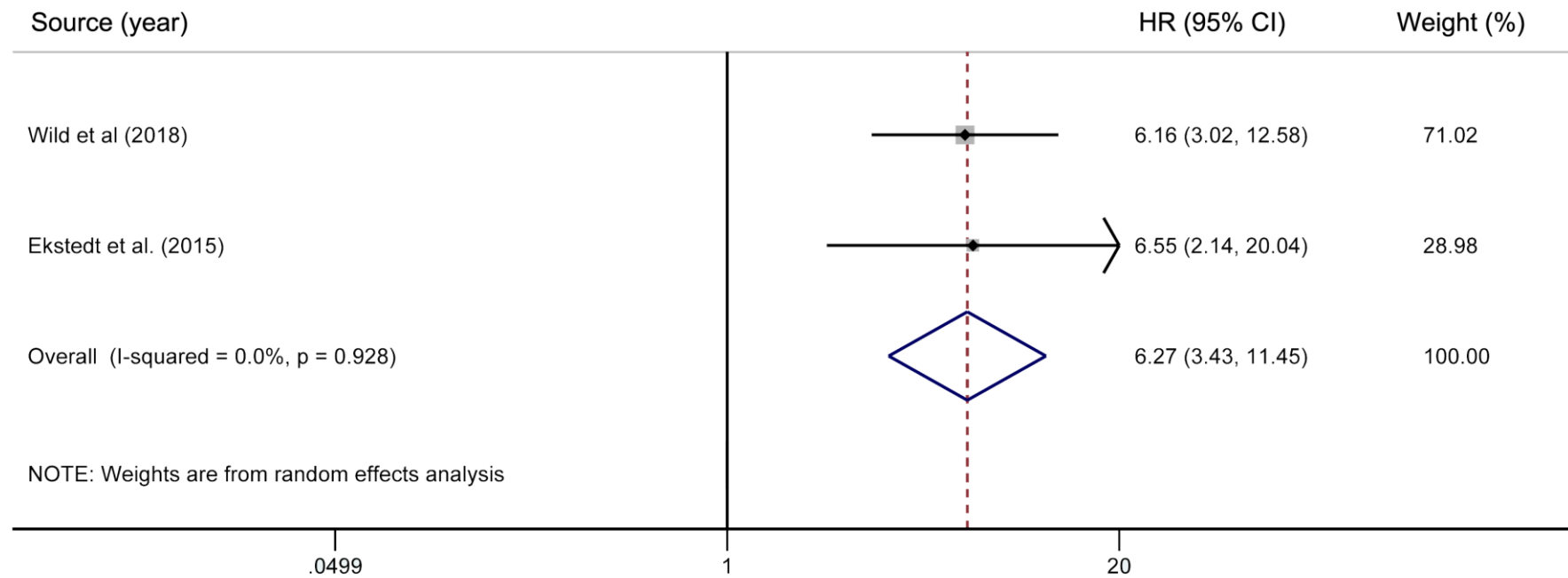
all-cause mortality

Figure S3. Results of meta-analysis on nonalcoholic fatty liver disease and hepatocellular carcinoma mortality. The squares represent the risk estimate for each individual study, with the area reflecting the weight assigned to the study. The horizontal line across each square represents the 95% CI. The diamond represents the summary risk estimate, with width representing 95% CI. HR, hazard ratio; CI, confidence interval.