ONLINE-ONLY SUPPLEMENTARY MATERIAL

Supplementary Figure 1. (A) Risk of bias summary for each eligible study as assessed by the Cochrane Collaboration's tool. (B) Risk of bias graph for all eligible studies as assessed by the Cochrane Collaboration's tool.

Supplementary Figure 2. Univariable meta-regression analyses. A meta-analysis of the association of age (A), male sex (B), body mass index (C), proportion of pre-existing diabetes (D), proportion of pre-existing hypertension (E), proportion of current smokers (F), or mean plasma LDL-cholesterol levels (G) with the risk of fatal and nonfatal CVD events (for the studies included in Figure 2).

Supplementary Figure 3. Meta-analysis estimates, given named study is omitted (for the studies included in Figure 2). The effect size was expressed as random-effects hazard ratio (HR) and 95% CIs for all studies.

Supplementary Figure 4. Funnel plot of standard error by log-hazard ratio for the risk of incident CVD events (for the studies included in Figure 2). P-values were assessed by the Egger's regression test.

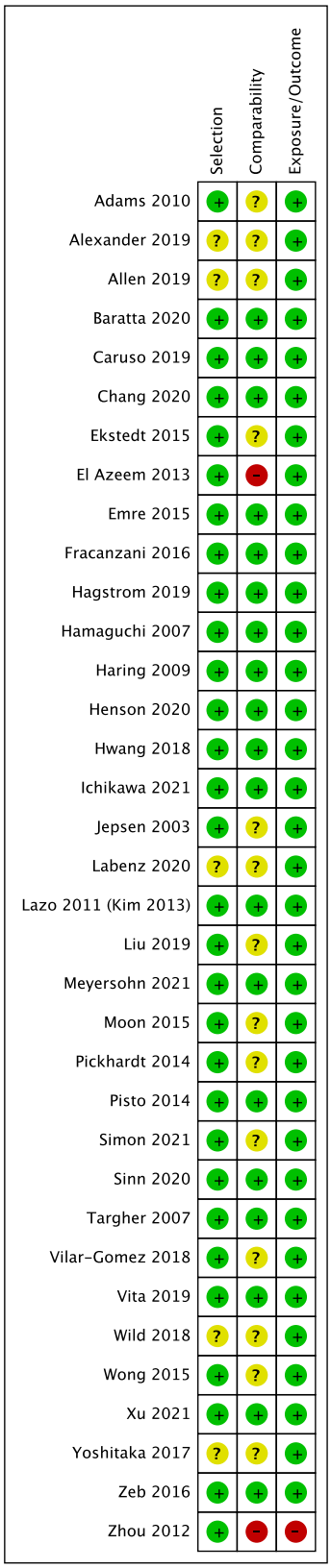
Supplementary Table 1. Syntax used through database searching on PubMed, Scopus or Web of Science (WOS).

Supplementary Table 2. Studies excluded at the eligibility step of PRISMA diagram (n=10 studies).

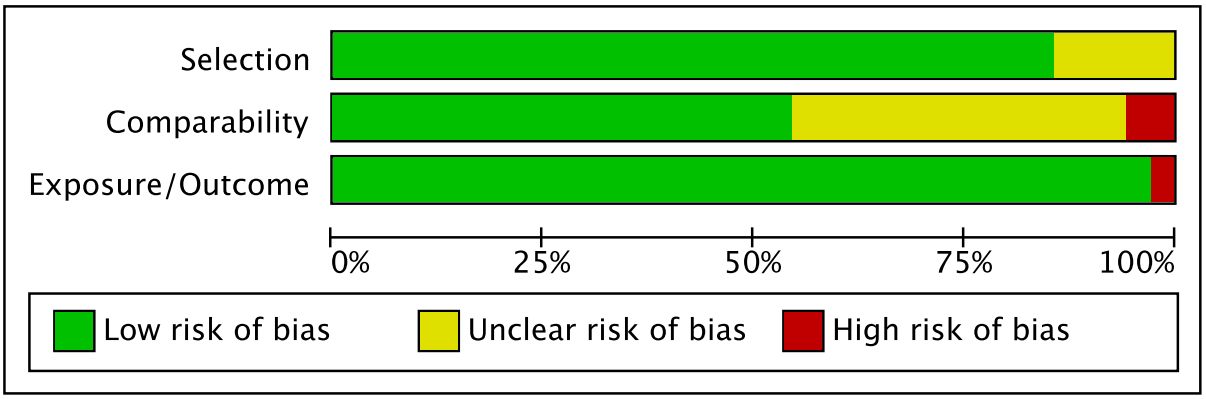
Supplementary Table 3. Eligible observational studies assessing the association between NAFLD and risk of fatal or non-fatal CVD events, ordered by publication year (n=36 studies).

Supplementary Table 4. Newcastle-Ottawa Quality Assessment Scale for the studies included in the meta-analysis.

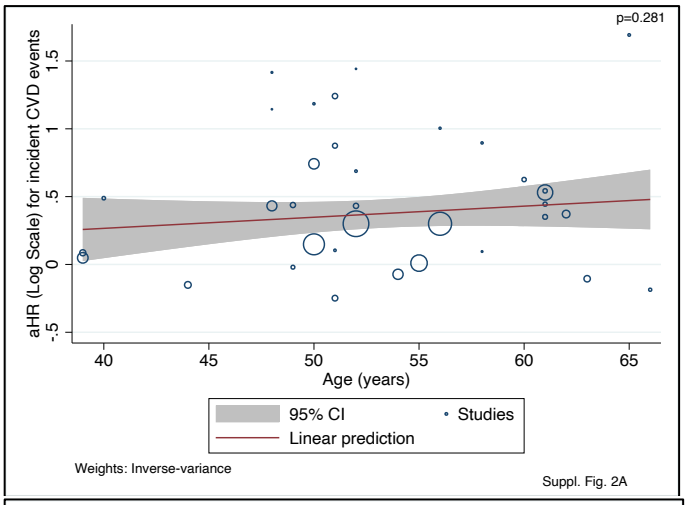
Supplementary Figure 1A. Risk of bias summary for each eligible study as assessed by Cochrane Collaboration's tool

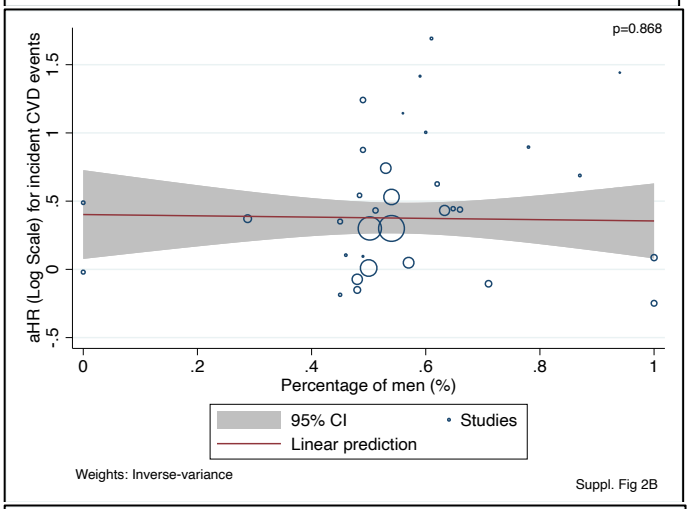


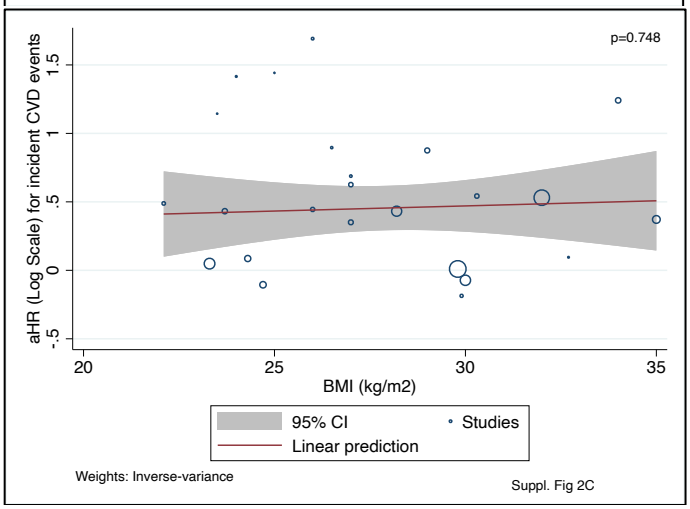
Supplementary Figure 1B.
Risk of bias graph for all eligible study as assessed by Cochrane Collaboration's tool

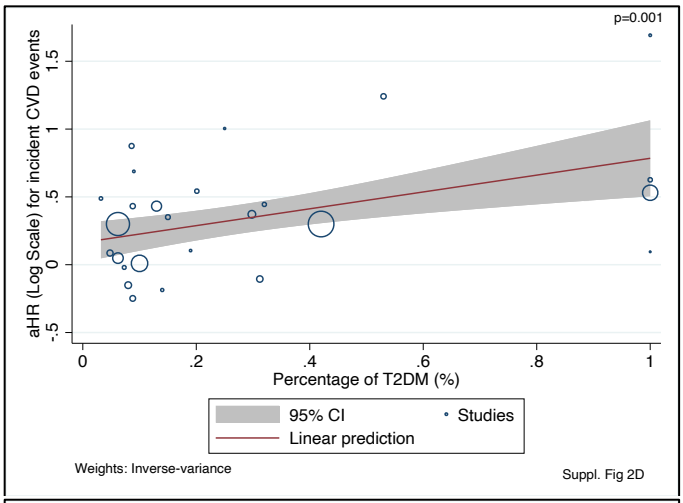


Supplementary Figure 2. Univariable meta-regression analyses. A meta-analysis of the association of age (A), male sex (B), body mass index (C), proportion of pre-existing diabetes (D), proportion of pre-existing hypertension (E), proportion of current smokers (F), or mean plasma LDL-cholesterol levels (G) with the risk of fatal and nonfatal CVD events (for the studies included in Figure 2).

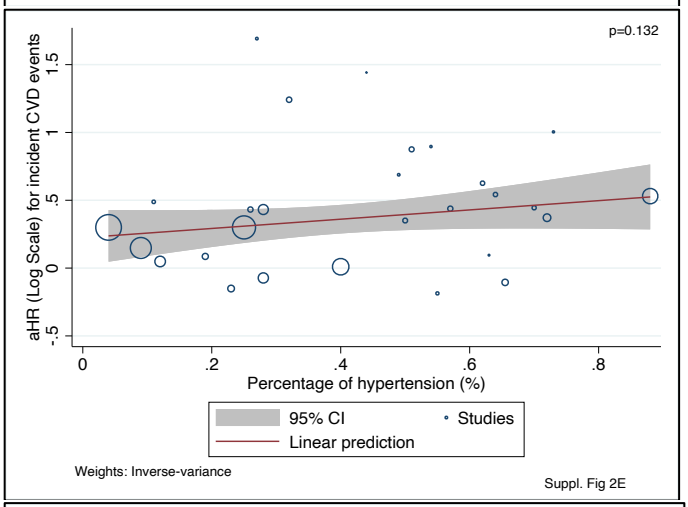




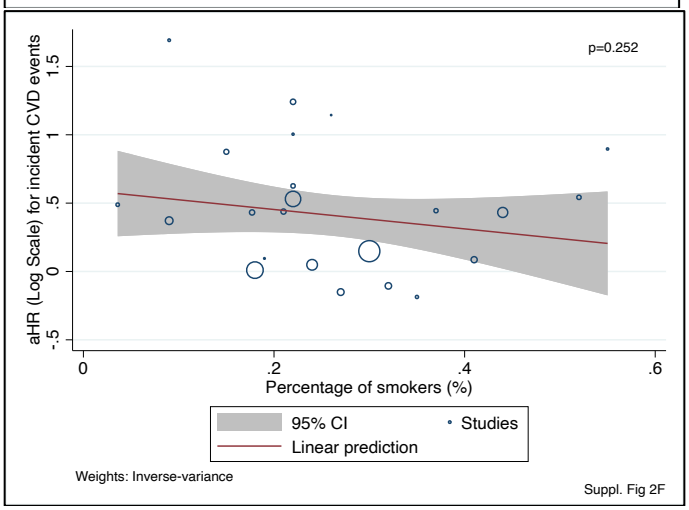




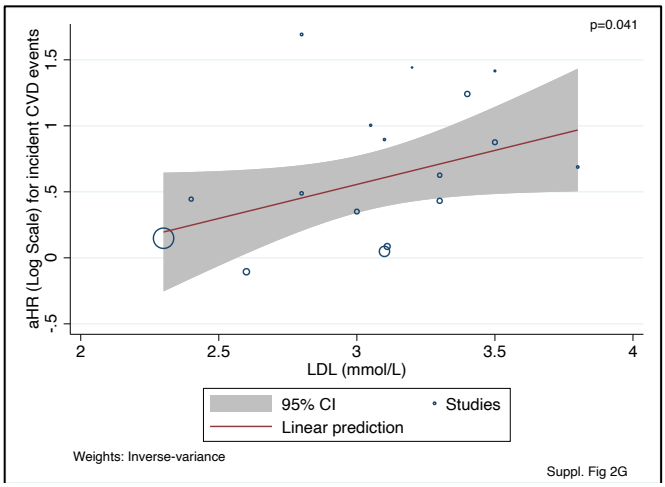
Suppl. Fig 2D



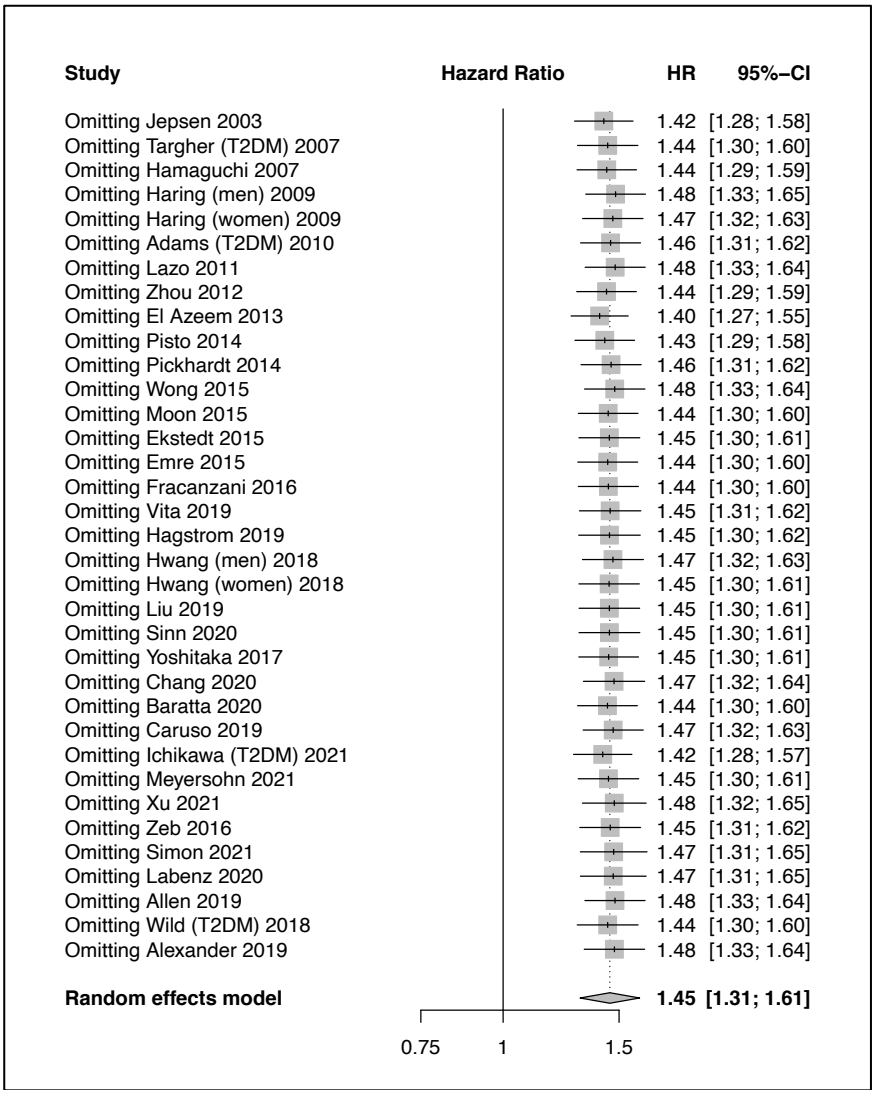
Suppl. Fig 2E



Suppl. Fig 2F


p=0.041
aHR (Log Scale) for incident CVD events
-.5
0
.5
1
1.5
2
2.5
3
3.5
4
LDL (mmol/L)
95% CI
Studies
Linear prediction
Weights: Inverse-variance
Suppl. Fig 2G

Supplementary Figure 3. Meta-analysis estimates, given named study is omitted (for the 33 studies included in Figure 2). The effect size was expressed as random-effects hazard ratio (HR) and 95% CIs for all studies.



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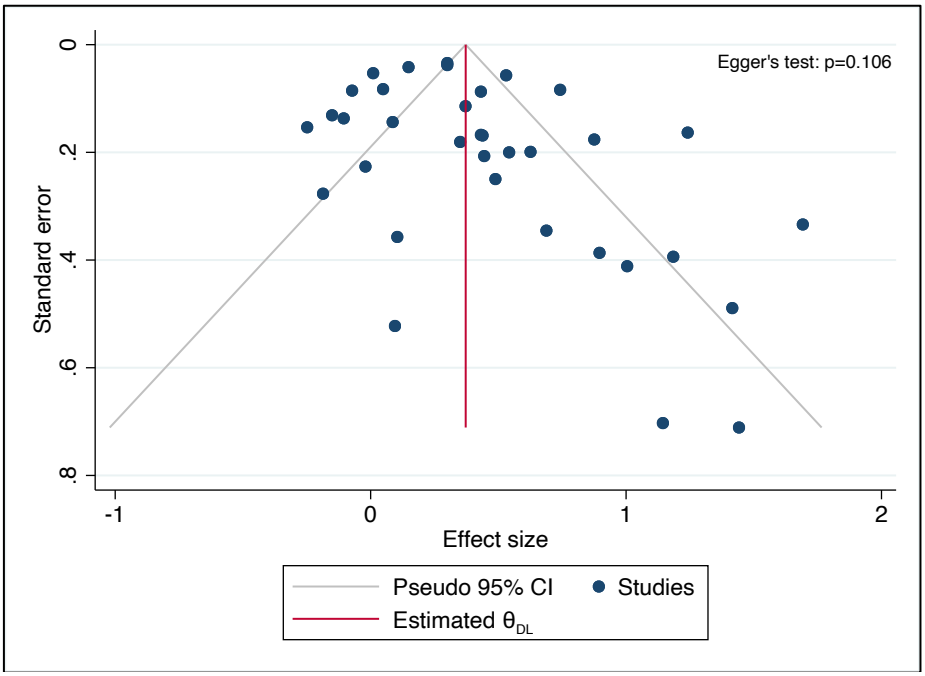

Supplementary Table 1. Syntax used through database searching on PubMed, Scopus or Web of Science (WOS).

PubMed <up to July 1, 2021> (LIMIT-TO (AGE, "Adult: +18 years")) (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (EXACTKEYWORD , "Humans"))

#1	"NAFLD" AND "risk of cardiovascular disease"	984
#2	"fatty liver" AND "risk of cardiovascular disease"	1428
#3	"nonalcoholic steatohepatitis" AND "risk of cardiovascular disease"	943
#4	"NASH" AND "risk of cardiovascular disease"	265
#5	"NAFLD" AND "risk of CVD"	124
#6	"fatty liver" AND "risk of CVD"	161
#7	"nonalcoholic steatohepatitis" AND "risk of CVD"	116
#8	"NASH" AND "risk of CVD"	28
#9	"NAFLD" AND "risk of incident CVD events"	20
#10	"fatty liver" AND "risk of incident CVD events"	27
#11	"nonalcoholic steatohepatitis" AND "risk of incident CVD events"	20
#12	"NASH" AND "risk of incident CVD events"	4
#13	"NAFLD" AND "risk of incidence of CVD events"	20
#14	"fatty liver" AND "risk of incidence of CVD events"	27
#15	"nonalcoholic steatohepatitis" AND "incidence of CVD events"	4
#16	"NASH" AND "risk of incidence of CVD events"	20

Scopus <up to July 1, 2021> (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SUBJAREA , "MEDI")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (EXACTKEYWORD , "Humans"))

#1	"NAFLD" AND "risk of cardiovascular disease"	887
#2	"fatty liver" AND "risk of cardiovascular disease"	1825
#3	"nonalcoholic steatohepatitis" AND "risk of cardiovascular disease"	688
#4	"NASH" AND "risk of cardiovascular disease"	1107
#5	"NAFLD" AND "risk of CVD"	31
#6	"fatty liver" AND "risk of CVD"	82
#7	"nonalcoholic steatohepatitis" AND "risk of CVD"	18
#8	"NASH" AND "risk of CVD"	82
#9	"NAFLD" AND "risk of incident CVD events"	2
#10	"fatty liver" AND "risk of incident CVD events"	3
#11	"nonalcoholic steatohepatitis" AND "risk of incident CVD events"	1
#12	"NASH" AND "risk of incident CVD events"	1
#13	"NAFLD" AND "risk of incidence of CVD events"	2
#14	"fatty liver" AND "risk of incidence of CVD events"	3
#15	"nonalcoholic steatohepatitis" AND "incidence of CVD events"	1
#16	"NASH" AND "risk of incidence of CVD events"	1

Web of Science <up to July 1, 2021> (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English"))

#1	"NAFLD" AND "risk of cardiovascular disease"	1491
#2	"fatty liver" AND "risk of cardiovascular disease"	3212
#3	"nonalcoholic steatohepatitis" AND "risk of cardiovascular disease"	635
#4	"NASH" AND "risk of cardiovascular disease"	471
#5	"NAFLD" AND "risk of CVD"	221
#6	"fatty liver" AND "risk of CVD"	403
#7	"nonalcoholic steatohepatitis" AND "risk of CVD"	66
#8	"NASH" AND "risk of CVD"	57
#9	"NAFLD" AND "risk of incident CVD events"	12
#10	"fatty liver AND "risk of incident CVD events"	19
#11	"nonalcoholic steatohepatitis" AND "risk of incident CVD events"	2
#12	"NASH" AND "risk of incident CVD events"	1
#13	"NAFLD" AND "risk of incidence of CVD events"	12
#14	"fatty liver" AND "risk of incidence of CVD events"	19
#15	"nonalcoholic steatohepatitis" AND "incidence of CVD events"	2
#16	"NASH" AND "risk of incidence of CVD events"	1

Supplementary Table 2. Studies excluded at the eligibility step of PRISMA diagram (n=10 studies).

Author, year, (PMIDs)	Main reasons for exclusion
Käräjämäki et al. 2017 (PMID: 27423871)	Same cohort of the study by Pisto et al. 2014 already included in the meta-analysis
Shah et al. 2017 (PMID: 28330662)	Same cohort of the study by Zeb et al. already included in the meta-analysis
Hagström et al. 2017 (PMID: 28803953)	Same cohort of the study by Hagström et al. 2019 already included in the meta-analysis
Baik et al. 2019 (PMID: 30763931)	Low quality study with unsatisfactory inclusion criteria
Lauridsen et al. 2019 (PMID: 29228164)	Unsatisfactory study design (cross-sectional)
Niriella et al. 2020 (PMID: 31472085)	Unsatisfactory study design (low quality study with very few CVD events)
Motamed et al. 2020 (PMID: 32742574)	Unsatisfactory study design (low quality study with unclear study design)
Paik et al. 2020 (PMID: 31782543)	Same cohort of the NHANES 1988-1994 by Lazo & Kim et al. studies already included in the meta-analysis
Lee et al. 2020 (PMID: 33348045)	Unsatisfactory inclusion criteria (use of fatty liver index for the diagnosis of NAFLD)
Niriella et al. 2021 (PMID: 33534815)	Unsatisfactory study design (low quality study with very few CVD events)

Supplementary Table 3. Eligible observational studies assessing the association between NAFLD and risk of fatal or non-fatal CVD events, ordered by publication year (n=36).

Author, year, (PMID)	Study Characteristics	Diagnosis of NAFLD (number of patients with NAFLD)	CVD Outcomes (number of events)	Main Results	Covariate Adjustments	NOS
Jepsen et al. 2003 (PMID: 14696473)	Retrospective hospital- based cohort: 1,804 Danish adult patients discharged with a diagnosis of NAFLD from a Danish hospital; (53% men). Mean follow-up: 6.4 years	Ultrasonography (n=1,804)	All-cause and CVD mortality (n=197)	Compared to the general population matched by age, sex and county, patients with NAFLD had a higher risk of CVD death (aHR 2.10, 95% CI 1.80-2.50)	General population comprised all those of the same age and sex living in the same county as each patient with NAFLD at baseline	8
Targher et al. 2007 (PMID: 17519430)	Prospective cohort study: 2,103 Italian outpatients with T2DM (mean age 60 years; mean BMI 27 kg/m^2; 62% men). Mean follow-up: 6.5 years	Ultrasonography (n=1,417)	Fatal and non-fatal CVD events (i.e. myocardial infarction, ischaemic stroke, coronary revascularizations or CVD death) (n=384 CVD events, 121 of whom had fatal events)	Compared to those without NAFLD, patients with NAFLD had a higher risk of fatal and non-fatal CVD events (aHR 1.87; 95% CI 1.21-2.64)	Age, sex, smoking status, diabetes duration, HbA1c, LDL-cholesterol, medication use (i.e., hypoglycemic, anti-hypertensive or lipid-lowering agents), metabolic syndrome	9
Hamaguchi et al. 2007 (PMID: 17461452)	Population-based cohort study: 1,637 Japanese individuals (mean age 48 years; mean BMI 24 kg/m^2; 59% men) who performed a health check-up program). Mean follow-up: 5 years:	Ultrasonography (n=312)	Non-fatal CVD events (unstable angina, myocardial infarction or ischaemic/hemorrhagic strokes) (n=22)	Compared to those without NAFLD, patients with NAFLD had a higher risk of non-fatal CVD events (aHR 4.12; 95% CI 1.58-10.75)	Age, sex, blood pressure, smoking status, LDL-cholesterol, metabolic syndrome	9
Haring et al. 2009 (PMID: 19670414)	Population-based cohort study: 4,160 German individuals (mean age 50 years; mean BMI 24 kg/m^2; 59% men; 8% with T2DM) from the Study of Health in Pomerania (SHIP), after excluding those with previous hepatic disease. Median follow-up: 7.3 years	Ultrasonography and GGT levels (n=251 among men; n=165 among women)	All-cause and CVD mortality (n=307 CVD deaths)	Compared to those without NAFLD, patients with NAFLD did not have a higher risk of fatal CVD events (men: aHR 0.78, 95%CI 0.57-1.04; women aHR 0.98, 95%CI 0.63-1.53). Patients with severe forms of NAFLD (based on upper quintile of GGT levels) had a higher risk of fatal CVD events compared to those in the lowest quintile of GGT levels (men: aHR 2.41, 95%CI 1.05-5.53; women aHR 1.41, 95%CI 0.32-6.21)	Age, sex, waist circumference, alcohol consumption, physical activity, educational level, civil status, equalized income, functional comorbidity index	9
Adams et al. 2010 (PMID 20145609)	Retrospective cohort study: 337 US outpatients with T2DM (mean age 58 years; mean BMI 33 kg/m^2; 49% men) from the Olmsted county, between 1980 and 2000, after excluding those with known liver diseases. Mean follow-up: 10.9 years	Ultrasonography, computed tomography or biopsy (only in a subset of patients) (n=116)	All-cause and CVD mortality (n=36 CVD deaths)	Compared to those without NAFLD, patients with NAFLD did not have a higher risk of fatal CVD events (aHR 1.10, 95% CI 0.40-3.10)	Age, sex, duration of diabetes, obesity	8
Lazo et al. 2011 (PMID: 22102439)	Population-based study: 11,371 US individuals (mean age 44 years; 48% men; 8% with T2DM) from the NHANES 1988-94. Mean follow-up: 14.5 years	Ultrasonography (n=2,515)	All-cause and cause-specific mortality (n=1,836 total deaths, 716 of which were CVD deaths)	Compared to those without NAFLD, patients with NAFLD did not have a higher risk of fatal CVD events (aHR 0.86, 95% CI 0.67-1.12)	Age, sex, BMI, ethnicity, education, smoking status, alcohol consumption, physical activity, hypertension, dyslipidemia, T2DM	9

Zhou et al. 2012 (PMID: 22356310)	Population-based cohort study: 3,324 Chinese individuals without known liver diseases. Median follow-up: 4 years	Ultrasonography (n=467)	All-cause and CVD mortality (n=29 CVD deaths)	Compared to those without NAFLD, patients with NAFLD had a higher risk of fatal CVD events (uHR 3.27, 95% CI 1.57-7.07)	None	5
El Azeem et al. 2013 (PMID: 24198448)	Prospective cohort study: 1,150 Egyptian individuals (mean age 51 years; mean BMI 34 kg/m^2; 49% men; 53% with T2DM) with normal liver function and without prior CVD Mean follow-up: 3 years	Ultrasonography (n=268)	Non-fatal CVD events (unstable angina, myocardial infarction, coronary revascularizations or ischaemic/hemorrhagic strokes) (n=246)	Compared to those without NAFLD, patients with NAFLD had a higher risk of non-fatal CVD events (uHR 3.46, 95% CI 2.51-4.76)	None	6
Kim et al. 2013 (PMID: 23175136)	Population-based cohort study: 11,154 US individuals (mean age 44 years; mean BMI 27 Kg/m^2; 48% men; 6% with T2DM) from the NHANES 1988-94. Mean follow-up: 14.5 years NB: This is the same sample included in the study of Lazo et al, but data of this study were used only for analysis of severity	Ultrasonography (n=4,083)	All-cause and CVD mortality (n=1,795 total deaths, 673 of which were CVD deaths	Compared to NAFLD patients with NFS ≤0.676, NAFLD patients with NFS >0.676 had a higher risk of CVD deaths (aHR 3.46, 95% CI 1.91-6.27)	Age, sex, ethnicity, education, income, T2DM, hypertension, pre-existing CVD, medications, smoking status, waist circumference, alcohol consumption, caffeine consumption, dyslipidemia, transferrin saturation, plasma C-reactive protein	9
Pisto et al. 2014 (PMID: 24650811)	Prospective cohort study: 988 Finnish individuals (mean age 51 years; mean BMI 29 kg/m^2; 49% men; 8.6% with T2DM) from the Opera Study. Mean follow-up: 17.7 years	Ultrasonography (n=268)	Fatal and non-fatal CVD events (unstable angina, myocardial infarction, coronary revascularizations or ischaemic stroke) (n=169 CVD events, 54 of which were fatal)	Compared to those without NAFLD, patients with NAFLD had a higher risk of fatal and non-fatal CVD events (aHR 2.40, 95% CI 1.70-3.39). However, patients with severe NAFLD on ultrasonography , compared to those with no NAFLD, did not have a higher risk of CVD evets (aHR 1.49, 95% CI 0.93-2.39)	Age, sex, BMI, study group, smoking status, alcohol consumption, LDL-cholesterol, blood pressure, insulin resistance (by QUICKI index)	8
Pickhardt et al. 2014 (PMID: 24660702)	Retrospective cohort study: 4,412 US consecutive adults (mean age 51 years; 46% men; 19% with T2DM) after exclusion of those with known liver diseases or <1 year of follow-up. Mean follow-up: 7.5 years	Computed tomography (n=503)	Non-fatal CVD events (myocardial infarction, stroke, transient ischemic attacks, coronary revascularizations) (n=73)	Compared to those without NAFLD, patients with NAFLD did not have a higher risk of non-fatal CVD events (aHR 1.11, 95% CI 0.55-2.23)	Age, sex, diabetes, obesity, serum transaminases	7
Wong et al. 2015 (PMID: 26406278)	Prospective cohort study: 612 Chinese consecutive patients (mean age 63 years; mean BMI 24.7 kg/m^2; 71% men; 31% with T2DM) undergoing coronary angiograms without known liver disease	Ultrasonography (n=356)	Fatal and non-fatal CVD events (death, heart failure or secondary coronary revascularizations) (n=225 CVD events, 106 of which were fatal)	Compared to those without NAFLD, patients with NAFLD did not have a higher risk of CVD events (aHR 0.90, 95% CI 0.69-1.18)	Age and sex	7
Moon et al. 2015 (PMID: 24904182)	Prospective cohort study: 815 South Korean individuals (mean age 52 years; mean BMI 25 kg/m^2; 94% men). Mean follow-up: 4.2 years	Ultrasonography and positron emission tomography (n=394)	Non-fatal CVD events (angina, myocardial infarction, coronary revascularizations) (n=9)	Compared to those without NAFLD, patients with severe forms of NAFLD had a higher risk of CVD events (aHR 4.23, 95% CI 1.05-17.04)	Age, sex, BMI, plasma triglycerides	6

Ekstedt et al. 2015 (PMID: 25125077)	Retrospective cohort study: 229 Swedish patients (mean age 49 years; 66% men) with NAFLD and elevated serum liver enzyme levels. Mean follow-up: 26.4 years	Biopsy (n=229; 49% with NASH)	All-cause and CVD mortality (n=96 total deaths, 41 of which were CVD deaths)	Compared to a reference population, patients with NAFLD had a higher risk of CVD events (aHR 1.55, 95% CI 1.11-2.15). In addition, those with F3-F4 fibrosis had the highest risk of CVD events (aHR 4.36, 95% CI 2.29-8.29)	Reference population comprised all those of the same age and sex living in the same county as each patient with NAFLD at baseline	7
Emre et al. 2015 (PMID: 26506122)	Retrospective hospital-based cohort study: 186 consecutive Turkish non-diabetic patients (mean age 58 years; mean BMI 26.5 Kg/m^2; 78% men) undergoing primary percutaneous coronary interventions for ST-segment elevation myocardial infarction after excluding those with known liver diseases	Ultrasonography (n=75)	In-hospital CVD events (myocardial infarction, acute heart failure or death) (n=32 CVD events, 8 of which were fatal)	Compared to those without NAFLD, patients with moderate-severe NAFLD had a higher risk of in-hospital CVD events (aHR 2.45, 95% CI 1.07-4.87)	Age, sex, BMI, total cholesterol, HDL-cholesterol, triglycerides, presence of anterior wall infarction, multi-vessel coronary disease	8
Zeb et al. 2016 (PMID: 27102512)	Prospective cohort study: 4,119 US individuals (mean age 61 years; 45% men; 15% with T2DM) without free of CVD and known liver diseases at baseline from The Multi-Ethnic Study of Atherosclerosis (MESA). Median follow-up: 7.6 years	Computed tomography (n=728)	All-cause mortality and non-fatal CVD events (angina, myocardial infarction, resuscitated cardiac arrest or coronary revascularizations) (n=253 deaths; n=209 non-fatal CVD events)	Compared to those without NAFLD, patients with NAFLD had a higher risk of CVD events (aHR 1.42, 95% CI 1.00-2.03)	Age, sex, BMI, ethnicity, T2DM, hypertension, lipids, smoking status, family history of CHD, statin use, C-reactive protein, coronary artery calcium score on cardiac computed tomography	9
Fracanzani et al. 2016 (PMID: 26803429)	Prospective cohort study: 375 Italian patients (mean age 52 years; mean BMI 27 Kg/m^2; 87% men; 9% with T2DM). Mean follow-up: 10 years	Ultrasonography and biopsy (in a subset of patients) (n=125)	Non-fatal CVD events (acute coronary syndrome, coronary revascularizations, ischaemic stroke or transitory ischaemic attacks) (n=35)	Compared to those without NAFLD, patients with NAFLD had a higher risk of non-fatal CVD events (aHR 1.99, 95% CI 1.01-3.91)	Sex, age, smoking status, diabetes, hypertension, dyslipidemia, carotid atherosclerotic plaques on ultrasonography	9
Yoshitaka et al. 2017 (PMID: 28471965)	Post-hoc analysis of a prospective cohort study: 1,647 Japanese individuals (mean age 48 years; mean BMI 23.5 Kg/m^2, 56% men). Mean follow-up: 6 years	Ultrasonography (n=312)	Non-fatal CVD events (angina, myocardial infarction, ischaemic/hemorrhagic strokes) (n=22)	Compared to those without NAFLD, patients with NAFLD did not have a higher risk of non-fatal CVD events (aHR 3.14, 95% CI 0.84-13.2).	Age, sex, smoking status, exercise, hypertension, diabetes, dyslipidemia	6
Hwang et al. 2018 (PMID: 29158157)	Prospective cohort study: 165,131 South Korean men (mean age 39 years; mean BMI 24 Kg/m^2; 4.8% with T2DM) and 153,093 women (mean age 40 years; mean BMI 22 Kg/m^2; 3.2% with T2DM) underwent comprehensive annual or biennial health examinations. Mean follow-up: 5.7 years	Ultrasonography (n=62,680 men and 20,219 women)	CVD mortality (n=242)	Among men, when compared to those without NAFLD, patients with NAFLD did not have a higher risk of CVD mortality (aHR 1.09, 95% CI 0.82-1.44). Conversely, among women, the risk of CVD mortality was higher in NAFLD patients (aHR 1.63, 95% CI 1.00-2.66)	Age, sex, BMI, smoking status, alcohol consumption, physical activity, diabetes, hypertension, hypercholesterolemia	9
Wild et al. 2018 (PMID:	Retrospective cohort study: 134,368 Scottish individuals with	ICD-10 (n=1,452)	Fatal CVD events (coronary heart disease, cerebrovascular	Compared to those without NAFLD, patients with NAFLD had a higher risk of	Age, sex, socioeconomic status, smoking status, hypertension,	6

29167212)	T2DM (mean age 61 years; mean BMI 32 Kg/m^2; 54% men). Mean follow-up: 4.3 years		disease, heart failure or sudden cardiac death) (n=4,469)	non-fatal CVD events (aHR 1.70, 95% CI 1.52-1.90)	dyslipidemia, HbA1c, medication use	
Vilar-Gomez et al. 2018 (PMID: 29733831)	Prospective multi-national study: 458 patients with biopsy-confirmed NAFLD with bridging fibrosis (F3, n=159) or compensated cirrhosis (n=222). Mean follow-up: 5.5 years	Biopsy (n=458)	Cardiovascular, cerebrovascular or arterial peripheral diseases (n=14)	Compared to those with cirrhosis, patients with bridging fibrosis had a higher risk of MACE (aHR 4.0, 95% CI 1.4-12.5)	Age, sex, BMI, diabetes, LDL-cholesterol	7
Vita et al. 2019 (PMID: 30835188)	Retrospective cohort study: 886 US patients (mean age 62 years; mean BMI 35 Kg/m^2; 29% men; 30% with T2DM) without evidence of obstructive coronary artery disease and preserved left ventricular ejection fraction (≥40%) at a clinical rest and stress myocardial perfusion PET/CT. Mean follow-up: 5.6 years	Computed tomography (n=125)	Fatal and non-fatal CVD (all-cause mortality, non-fatal myocardial infarction, coronary revascularizations, or hospitalization for heart failure) (n=130)	Compared to those without NAFLD, patients with NAFLD had a higher risk of MACE (aHR 1.45, 95% CI 1.08-1.69)	Age, sex, BMI, hypertension, smoking status, left ventricular ejection fraction, abnormal coronary flow reserve	8
Hagström et al. 2019 (PMID: 30253056)	Prospective cohort study: 603 Swedish biopsy-proven NAFLD patients free of baseline CVD and matched (1:10, by age, sex and municipality) to 6,269 population control (mean age 48 years; mean BMI 28 Kg/m^2; 63% men; 13% with T2DM). Mean follow-up:18.6 years	Biopsy (n=603)	Non-fatal CVD events (acute ischaemic heart disease or ischaemic stroke) (n=1,493)	Compared to reference population, patients with NAFLD had a higher risk of non-fatal CVD events (aHR 1.54, 95% CI 1.30-1.83)	Control population was matched by age, sex, and municipality to NAFLD cases	7
Liu et al. 2019 (PMID: 30829918)	Matched case-control study: 324 Chinese patients (mean age 61 years; mean BMI 26 Kg/m^2, 65% men; 32% with T2DM); in particular, 162 cases and 162 controls matched by age and sex. Follow-up: 3 years	Ultrasonopgraphy (n=64)	Fatal and non-fatal CVD events (all-cause death, mainly caused by CVDs, non-fatal myocardial infarction and stroke) (n=162)	Compared to those without NAFLD, patients with NAFLD had a higher risk of CVD events (aHR 1.56, 95% CI 1.04-2.34)	Age, sex, hypertension, diabetes, left ventricular ejection fraction, creatinine, high-sensitivity C-reactive protein, statin use and Gensini score	7
Allen et al. 2019 (PMID: 31577570)	Community-based cohort study: 19,078 US adults (mean age 54 years; mean BMI 30 Kg/m^2; 48% men) with NAFLD in Olmsted County, Minnesota, between 1997 and 2014 and selected an age- and sex-matched (1:4) referent cohort from the general population. Mean follow-up: 7 years	ICD-9 (n=3,869)	Non-fatal CVD events (angina, myocardial infarction, and ischaemic stroke) (n=3,851)	Compared to those without NAFLD, patients with NAFLD did not have a higher risk of non-fatal CVD events (aHR 0.93, 95% CI 0.78-1.09)	Age, sex, county	6
Caruso et al. 2019 (PMID: 31227533)	Prospective cohort study: 1,053 Italian adult individuals randomly selected from the electoral rolls of the population of Castellana Grotte (mean age	Ultrasonography (n=457)	CVD mortality (n=95)	Compared to those without NAFLD, patients with NAFLD did not have a higher risk of CVD death (aHR 0.83, 95% CI 0.48-1.42)	Age, sex, smoking status, waist circumference, blood pressure, diabetes, daily energy intake, prior myocardial infarction,	8

	66 years; mean BMI 30 Kg/m^2; 45% men; 14% with T2DM) with no excessive alcohol consumption. Median follow-up: 12 years					
Alexander et al. 2019 (PMID: 31594780)	Retrospective multicenter cohort study: 4,751,086 individuals (mean age 55 years; mean BMI 30 Kg/m^2; 50% men; 10% with T2DM) in primary care from four European countries (Italy, Netherlands, Spain and UK). Mean follow-up: 5 years	ICD-10 (n=120,795)	Non-fatal CVD events (myocardial infarction and ischemic/undetermined strokes) (n=68,858 for acute myocardial infarction and n=136,188 for stroke)	Compared to those without NAFLD, patients with NAFLD did not have a higher risk non-fatal CVD events (aHR 1.01, 95% CI 0.91-1.12 for acute myocardial infarction; aHR 1.04, 95% CI 0.99-1. 09 for stroke)	Age, sex, smoking status, diabetes, hypertension, statin use	6
Sinn et al. 2020 (PMID: 31512278)	Retrospective cohort study: 111,492 South Korean adults (mean age 52 years; mean BMI 24 Kg/m^2, 51% men; 8.8% with T2DM) without history of CVD, liver disease, or cancer at baseline who participated in a regular health screening exam between 2003 and 2013. Mean follow-up: 10 years	Ultrasonopgraphy (n=37,263)	Non-fatal myocardial infarction (n=183)	Compared to those without NAFLD, patients with NAFLD had a higher risk of myocardial infarction (aHR 1.54, 95% CI 1.11-2.14). In addition, NAFLD patients with NFS ≥1.455 had higher risk of myocardial infarction compared to those with NFS <1.455 (aHR 1.88, 95% CI 1.24-2.87)	Age, sex, BMI, year of visit, smoking status, systolic blood pressure, fasting glucose, LDL-cholesterol, medication use	8
Chang et al. 2020 (PMID: 31085337)	Prospective cohort study: 218,030 Chinese individuals (mean age 39 years; mean BMI 23 Kg/m^2, 57% men; 6.2% with T2DM) from the Kangbuk Samsung Health Study. In-hospital events	Ultrasonography (n=47,936)	CVD hospitalization (for ischaemic heart disease or ischaemic stroke) (n=1,097)	Compared to those without NAFLD, patients with NAFLD did not have a higher risk of CVD hospitalization (aHR 1.05, 95% CI 0.89-1.23)	Age, sex, center, year of screening examination, BMI, smoking, physical activity, educational level, total calorie intake, family history of CVD, diabetes, hypertension, LDL-cholesterol, medications, plasma high-sensitivity C-reactive protein, insulin resistance (HOMA-IR)	8
Henson et al. 2020 (PMID: 32043602)	Prospective cohort study: 285 US biopsy-proven NAFLD individuals (mean age 56 years; mean BMI 32 Kg/m^2; 56% men; 31% with T2DM) without pre-existing CVD. Mean follow-up: 5.2 years	Biopsy (n=285)	Fatal and non-fatal CVD events (defined as coronary artery disease, congestive heart failure, peripheral vascular disease, stroke, transient ischaemic attack, or a major adverse cardiac event, which included myocardial infarction, coronary revascularizations, or cardiac-related death) (n=26)	Compared to those without advanced fibrosis on histology, patients with advanced fibrosis (F3-F4) had a higher risk of CVD events (aHR 2.86, 95% CI 1.36-6.04)	Age, smoking status, diabetes, serum ALT, ALP, bilirubin, platelets, albumin, lipid profile, Framingham risk score	8
Baratta et al. 2020 (PMID: 31887443)	Prospective cohort study: 898 Italian outpatients with metabolic disorders from the PLINIO study (mean age 56 years; 60% men; 25% with T2DM). Mean follow-up: 3.5 years	Ultrasonography (n=643)	Fatal and non-fatal CVD events (fatal/nonfatal ischaemic stroke myocardial infarction, coronary or peripheral revascularizations, new-onset supraventricular arrhythmias and CVD death) (n=58)	Compared to those without NAFLD, patients with NAFLD had a higher risk of fatal and non-fatal CVD events (aHR 2.73, 95% CI 1.22-6.12). In addition, NAFLD patients with NFS >0.676 had higher risk of fatal and non-fatal CVD events compared to NAFLD patients with NFS<0.676 (aHR 2.53, 95% CI 1.05-	Age, sex, previous history of CVD, metabolic syndrome, smoking status, statin use	7

				5.27)		
Labenz et al. 2020 (PMID: 31797186)	Retrospective case-control cohort study: 44,096 German patients with NAFLD and matched (1:1) controls (mean age 56 years; 50% men; 6.2% with T2DM) in primary care. Mean follow-up: 10 years	ICD-10 (n=22,048)	Non-fatal CVD events (incidence of MI, CHD, AF, and stroke) (n=5,027)	Compared to those without NAFLD, patients with NAFLD had a higher risk of non-fatal CVD events (aHR 1.35, 95% CI 1.25-1.45)	Age, sex, diabetes, hypertension, dyslipidemia	6
Ichikawa et al. 2021 (PMID: 33413363)	Prospective cohort study: 529 Japanese patients with T2DM (mean age 65 years; mean BMI 26 Kg/m^2; 61% men) and no prior history of CVD undergoing coronary artery calcium score measurement. Mean follow-up: 4.4 years	Computed tomography (n=143)	Fatal and non-fatal CVD events (death, nonfatal myocardial infarction, late coronary revascularization, nonfatal stroke, or hospitalization for heart failure) (n=44)	Compared to those without NAFLD, patients with NAFLD had a higher risk of fatal and non-fatal CVD events (aHR 5.43, 95% CI 2.82-10.4)	Age, sex, hypertension, dyslipidemia, smoking status, obesity, coronary artery calcium scoring	7
Meyersohn et al. 2021 (PMID: 32707340)	A nested cohort study: 3,756 US patients (mean age 61 years; mean BMI 30 Kg/m^2; 48% men; 20% with T2DM) who underwent coronary computed tomography angiography. Mean follow-up: 25 years	Computed tomography (n=959)	Fatal and non-fatal CVD events (death from any cause, myocardial infarction, or hospitalization for unstable angina) (n=322)	Compared to those without NAFLD, patients with NAFLD had a higher risk of MACE events (aHR 1.72, 95% CI 1.16-2.54)	Age, sex, ASCVD (atherosclerotic cardiovascular disease) risk score, metabolic syndrome, presence of significant coronary stenoses	8
Xu et al. 2021 (PMID: 33272125)	Prospective cohort study: 79,905 Chinese participants free of history of stroke, cancer, or myocardial infarction were enrolled after excluding alcohol abuse and other liver diseases. Mean Follow-up: 10.3 years	Ultrasonography (n=24,874)	Non-fatal ischaemic stroke (n=3,490)	Compared to those without NAFLD, patients with NAFLD had a higher risk of incident ischaemic stroke (aHR 1.16, 95% CI 1.07-1.26)	Age, sex, BMI, physical activity, smoking status, hypertension, diabetes, dyslipidemia, medication use fasting glucose, plasma C-reactive protein	9
Simon et al. 2021 (PMID: 33037056)	Retrospective nationwide, matched cohort study: 10,568 Swedish patients with biopsy-proven NAFLD and 49,925 controls matched (1:5) for age, sex, calendar year and county (mean age 52 years; 54% men; 42% with T2DM). Mean follow-up: 14.2 years	Biopsy (n=10,568)	CVD mortality (n=6,938)	Compared to controls without NAFLD, patients with NAFLD had a higher risk of CVD mortality (aHR 1.35, 95% CI 1.26-1.44). In addition, compared to controls, patients with simple steatosis (aHR 1.25, 95% CI 1.16-1.35), NASH without fibrosis (aHR 1.66, 95% CI 1.38-2.01), non-cirrhotic fibrosis (aHR 1.40, 95% CI 1.17-1.69) or cirrhosis (aHR 2.11, 95% CI 163-2.73) had higher risk of CVD mortality	Age, sex, county, calendar year, education level, prior CVD, diabetes, obesity, hypertension, dyslipidemia	8

Abbreviations: aHR adjusted hazard ratio; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HOMA-IR, Homeostasis model assessment: insulin resistance; ICD, International Classification of Diseases; MetS, metabolic syndrome; MI, myocardial infarction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NHANES, National Health and Nutrition Examination Survey; NOS, Newcastle-Ottawa quality scale; T2DM, type 2 diabetes; uHR, unadjusted hazard ratio.

Note: For all studies reported in the table (unless where indicated), CVD mortality was defined as a combination of deaths from ischaemic heart disease or cerebrovascular disease. Some of the aforementioned studies were included only in the pooled secondary analysis examining the association between the severity of NAFLD and risk of fatal and nonfatal CVD events (as specified in Figure 3).

Supplementary Table 4. Newcastle-Ottawa Quality Assessment Scale (NOS) for the studies included in the meta-analysis.

Study	Selection	Comparability	Outcome/Exposure
Jepsen 2003	✸✸✸✸	✸	✸✸✸
Targher 2007	✸✸✸✸	✸✸	✸✸✸
Hamaguchi 2007	✸✸✸✸	✸✸	✸✸✸
Haring 2009	✸✸✸✸	✸✸	✸✸✸
Adams 2010	✸✸✸✸	✸	✸✸✸
Lazo 2011 (or Kim 2013)	✸✸✸✸	✸✸	✸✸✸
Zhou 2012	✸✸✸✸	✸	✸
El Azeem 2013	✸✸✸	✸	✸✸✸
Pisto 2014	✸✸✸	✸✸	✸✸✸
Pickhardt 2014	✸✸✸	✸	✸✸✸
Wong 2015	✸✸✸	✸	✸✸✸
Moon 2015	✸✸✸	✸	✸✸
Ekstedt 2015	✸✸✸	✸	✸✸✸
Emre 2015	✸✸✸	✸✸	✸✸✸
Zeb 2016	✸✸✸✸	✸✸	✸✸✸
Fracanzani 2016	✸✸✸✸	✸✸	✸✸✸
Henson 2020	✸✸✸	✸✸	✸✸✸
Vita 2019	✸✸✸	✸✸	✸✸✸
Hagström 2019	✸✸✸	✸✸	✸✸✸
Hwang 2018	✸✸✸✸	✸✸	✸✸✸
Vilar-Gomez 2018	✸✸✸	✸	✸✸
Liu 2019	✸✸✸	✸	✸✸✸
Sinn 2020	✸✸✸	✸✸	✸✸✸
Yoshitaka 2017	✸✸	✸	✸✸✸
Chang 2020	✸✸✸	✸✸	✸✸✸
Baratta 2020	✸✸✸	✸✸	✸✸
Caruso 2019	✸✸✸	✸✸	✸✸✸
Ichikawa 2021	✸✸✸	✸✸	✸✸
Meyersohn 2021	✸✸✸	✸✸	✸✸✸
Xu 2021	✸✸✸✸	✸✸	✸✸✸
Simon 2021	✸✸✸✸	✸	✸✸✸
Alexander 2019	✸✸	✸	✸✸✸
Labenz 2020	✸✸	✸	✸✸✸
Allen 2019	✸✸	✸	✸✸✸
Wild 2018	✸✸	✸	✸✸✸