Association of non-alcoholic fatty liver disease with cardiovascular disease and all cause death in patients with type 2 diabetes mellitus: nationwide population based study

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ABSTRACT

OBJECTIVE

To investigate the risk of non-alcoholic fatty liver disease (NAFLD) for cardiovascular disease and all cause death in patients with type 2 diabetes mellitus (T2DM).

DESIGN

Nationwide population based study.

SETTING

Longitudinal cohort study in Korea.

PARTICIPANTS

7 796 763 participants in the National Health Screening Programme in 2009 were divided into three groups based on NAFLD status: no NAFLD (fatty liver index<30); grade 1 NAFLD (30≤fatty liver index<60); and grade 2 NAFLD (fatty liver index≥60). Median follow-up was 8.13 years.

MAIN OUTCOME MEASURES

The primary outcome was incident cardiovascular disease (myocardial infarction, ischaemic stroke) or all cause death.

RESULTS

Of 7 796 763 participants, 6.49% (n=505 763) had T2DM. More patients with T2DM had grade 1 NAFLD (34.06%) and grade 2 NAFLD (26.73%) than those without T2DM (grade 1 NAFLD: 21.20%; grade 2 NAFLD: 10.02%). The incidence rate (per 1000 person years) of cardiovascular disease and all cause death increased in the order of no NAFLD, grade 1 NAFLD, and grade 2 NAFLD, and the incidence rates in patients with T2DM were higher than those in patients without T2DM. The five year absolute risk for cardiovascular disease and all cause death increased in the order of no NAFLD, grade 1 NAFLD, and grade 2 NAFLD in patients without and with T2DM (no NAFLD, without T2DM: 1.03, 95% confidence interval 1.02 to 1.04, and 1.25, 1.24 to 1.26, respectively; grade 1 NAFLD, without T2DM: 1.23, 1.22 to 1.25, and 1.50, 1.48 to 1.51, respectively; grade 2 NAFLD, without T2DM: 1.42, 1.40 to 1.45, and 2.09, 2.06 to 2.12, respectively; no NAFLD, with T2DM: 3.34, 3.27 to 3.41, and 3.68, 3.61 to 3.74, respectively; grade 1 NAFLD, with T2DM: 3.94, 3.87 to 4.02, and 4.25, 4.18 to 4.33, respectively; grade 2 NAFLD, with T2DM: 4.66, 4.54 to 4.78, and 5.91, 5.78 to 6.05, respectively). Patients with T2DM and without NAFLD had a higher five year absolute risk for cardiovascular disease and all cause death than those without T2DM and with grade 2 NAFLD. Risk differences for cardiovascular disease and all cause death between no NAFLD and grade 1 or grade 2 NAFLD were higher in patients with T2DM than in those without T2DM.

CONCLUSIONS

NAFLD in patients with T2DM seems to be associated with a higher risk of cardiovascular disease and all cause death, even in patients with mild NAFLD. Risk differences for cardiovascular disease and all cause death between the no NAFLD group and the grade 1 or grade 2 NAFLD groups were higher in patients with T2DM than in those without T2DM.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Non-alcoholic fatty liver disease and type 2 diabetes mellitus might have a synergistic association that contributes to cardiovascular risk in affected patients

Large scale, population based, longitudinal studies are needed that evaluate the association between non-alcoholic fatty liver disease and cardiovascular disease risk in patients with type 2 diabetes mellitus

WHAT THIS STUDY ADDS

Non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus seems to be associated with a higher risk of cardiovascular disease and all cause death, even in patients with a mild degree of fatty liver

Risk differences for cardiovascular disease and all cause death between patients without non-alcoholic fatty liver disease and those with grade 1 or grade 2 non-alcoholic fatty liver disease were higher in those with type 2 diabetes mellitus than in those without this condition

Non-alcoholic fatty liver disease screening and prevention could reduce the risk of cardiovascular disease and all cause death in patients with type 2 diabetes mellitus

Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing worldwide.[1 2] Many studies have found that NAFLD is associated with various metabolic disorders based on insulin resistance.[3-5] NAFLD is a global health problem because of its ability to cause liver related complications (such as cirrhosis and hepatocellular carcinoma) and cardiovascular disease.[6-13] Cardiovascular disease is one of the leading causes of death in patients with NAFLD.[14 15]

Type 2 diabetes mellitus (T2DM) is one of the most important risk factors for cardiovascular disease,[16 17] and is strongly associated with greater NAFLD prevalence and severity.[9 18] Many studies have described a complex bidirectional association between NAFLD and T2DM[9 10]—60-70% of patients with T2DM have NAFLD.[9] NAFLD and T2DM might have a synergistic association that contributes to cardiovascular risk in affected patients.[19] However, some studies have reported mixed results when examining the association between NAFLD and cardiovascular disease in patients with T2DM.[11 12 20 21] Although one study found no correlation between

NAFLD and cardiovascular disease,[11] a meta-analysis of 11 studies showed that patients with T2DM and NAFLD had double the risk of cardiovascular disease compared with those with T2DM but without NAFLD.[12] However, previous studies assessing the risk of cardiovascular disease in patients with T2DM and NAFLD have been limited by small sample sizes or cross sectional design. Large scale, population based, longitudinal studies are needed evaluating the association between NAFLD and cardiovascular disease risk in patients with T2DM. Therefore, the aim of this study was to evaluate the risk of NAFLD for cardiovascular disease and all cause death in patients with T2DM using a nationwide database.

Methods

Data source

This is a nationwide, population based cohort study that used data from the National Health Information Database, which is administered by the National Health Insurance Service with linkage to the National Health Screening Programme. The National Health Insurance Service is a single payer healthcare system that is managed by the Korean government and covers more than 97% of the Korean population. The National Health Information Database contains data on sociodemographic variables, diagnoses (defined by the international classification of diseases, 10th revision—ICD-10), prescriptions, and hospital visit dates. Medical interviews, anthropometric measurements, blood tests, urine tests, and additional assessments were included in the National Health Screening Programme. We obtained mortality data from the National Death Registry. The current study protocol (SSU-202003-HR-201-01) was approved by the institutional review board of Soongsil University. The requirement for informed consent was waived by the institutional review board because the dataset was deidentified to protect personal information.

Study design and participants

We selected 10 601 283 participants from the National Health Screening Programme in 2009. We excluded patients who were younger than 20 years (n=15 431); had type 1 diabetes mellitus (n=172 315); consumed ≥30 g/day alcohol and had chronic hepatitis B, chronic hepatitis C, liver cirrhosis, or hepatocellular carcinoma (n=1 766 863); had cardiovascular disease (myocardial infarction or ischaemic stroke; n=363 151); or who had missing data (n=455 454; supplementary figure S1). To overcome bias, we also excluded those who developed cardiovascular disease within one year (lag period; n=31 306). Finally, 7 796 763 participants were included and followed from baseline to the date of incident cardiovascular disease, all cause death, or until 31 December 2018. The median follow-up duration was 8.13 years.

Measurements

Anthropometric and laboratory data were obtained through the National Health Screening Programme. Blood pressure was measured while participants were seated. After an overnight fast of at least eight hours, venous blood samples were obtained to measure glucose, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, total cholesterol, triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and creatinine levels. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

We used a standardised self-assessment questionnaire to obtain information about smoking status, alcohol consumption, and regular exercise. Mild drinker was defined as drinking <30 g/day alcohol. Regular exercise was defined as moderate intensity activity performed for at least 30 min, five or more times per week, or high intensity activity performed for at least 20 min, three or more times per week. Low income was defined by the lowest income group or meeting criteria for medical aid benefit.

Definitions

T2DM was defined by fasting plasma glucose concentration ≥126 mg/dL or the presence of at least one prescription claim per year for antidiabetic drugs under ICD-10 codes E11-14. Hypertension was defined as blood pressure ≥140/90 mm Hg or the presence of at least one prescription claim per year for antihypertensive drugs under ICD-10 codes I10-13 or I15. Dyslipidemia was defined using ICD-10 code E78 and at least one claim per year for prescription of a lipid lowering agent, or a total cholesterol level ≥240 mg/dL. Obesity was defined as a body mass index ≥25. Abdominal obesity was defined as waist circumference ≥90 cm in men and ≥85 cm in women. Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2.

Fatty liver index was used to define hepatic steatosis and was calculated using the following equation: $(e^{0.953\times \ln(TG)+0.139\times \text{body mass index}+0.718\times \ln(GGT)+0.053\times \text{waist circumference}-15.745}) \div (1+e^{0.953\times \ln(TG)+0.139\times \text{body mass index}+0.718\times \ln(GGT)+0.053\times \text{waist circumference}-15.745})\times 100$, where TG=triglyceride and GGT= γ-glutamyl transferase.[22] NAFLD was defined as the presence of hepatic steatosis without viral hepatitis or excessive alcohol consumption (≥30 g/day). Because we excluded patients who consumed excessive alcohol and those with chronic hepatitis B or hepatitis C, we defined NAFLD by the presence of hepatic steatosis assessed by fatty liver index alone. Patients were divided into three groups: no NAFLD, fatty liver index<30; grade 1 NAFLD, 30≤fatty liver index<60; and grade 2 NAFLD, fatty liver index≥60.

Study outcomes

The endpoint of this study was the development of cardiovascular disease or all cause death. Cardiovascular disease was defined as myocardial infarction or ischaemic stroke. Myocardial infarction was defined as ICD-10 code I21 or I22 during hospital admission. Ischaemic stroke was defined as ICD-10 code I63 or I64 during hospital admission with claims

for brain magnetic resonance imaging or computed tomography.

Statistical analysis

Data for continuous variables are presented as means±standard deviation or geometric mean (95% confidence interval). Categorical variables are reported as number (%). Incidence rates are presented as the number of events occurring per 1000 person years. Hazard ratio and 95% confidence interval for cardiovascular disease or all cause death were estimated using a Cox proportional hazards model. The multivariable models were adjusted for basic factors (age, sex), personal characteristics (smoking status, alcohol consumption, physical activity, and low income), and history or condition of disease (hypertension, dyslipidemia, body mass index, diabetes mellitus, and estimated glomerular filtration rate). We constructed Kaplan-Meier survival curves to compare the cumulative incidence rate of cardiovascular disease or all cause death according to the presence of NAFLD. Subgroup analysis was performed under the categories of sex, smoking status, abdominal obesity, aspartate aminotransferase or alanine aminotransferase, income level, alcohol consumption, regular exercise, obesity, hypertension, dyslipidemia, chronic kidney disease, or γ-glutamyl transferase. Variance inflation factor was calculated to assess the collinearity assumption, with variance inflation factor <5 considered to indicate no significant collinearity. Statistical significance was defined as a two sided P value<0.05. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Patient and public involvement

No patients were involved in setting the research question or the outcome measures. No patients were involved in developing plans for design or implementation of the study. Patient and public involvement was not commonly used in our discipline in this region when we started the study.

Results

Table 1 and supplementary table S1 present the baseline characteristics of the study population. Of 7 796 763 participants, 6.49% (n=505 763) had T2DM; additionally, 22.04% had grade 1 NAFLD and 11.11% had grade 2 NAFLD (supplementary tables S1 and S2). More patients with T2DM had grade 1 NAFLD (34.06%) and grade 2 NAFLD (26.73%) than

Table 1 | Baseline characteristics of the study population

Characteristics	Total (n=7 796 763)	Without type 2 diabetes mellitus			With type 2 diabetes mellitus		
		No NAFLD (n=5 014 234)	Grade 1 NAFLD (n=1 546 035)	Grade 2 NAFLD (n=730 731)	No NAFLD (n=198 322)	Grade 1 NAFLD (n=172 257)	Grade 2 NAFLD (n=135 184)
Age, years	45.94±13.74	44.35±13.81	48.16±13.07	45.30±12.15	57.08±12.57	56.91±11.46	52.68±11.75
20-29	1 053 565 (13.51)	877 157 (17.49)	110 632 (7.16)	57 090 (7.81)	4779 (2.41)	1603 (0.93)	2304 (1.70)
30-39	1 589 009 (20.38)	1 016 399 (20.27)	327 512 (21.18)	206 776 (28.30)	12 057 (6.08)	9,949 (5.78)	16 316 (12.07)
40-49	2 128 010 (27.29)	1 400 149 (27.92)	411 094 (26.59)	212 256 (29.05)	35 860 (18.08)	33 142 (19.24)	35 509 (26.27)
50-59	1 611 415 (20.67)	948 858 (18.92)	363 885 (23.54)	148 967 (20.39)	55 643 (28.06)	52 903 (30.71)	41 159 (30.45)
60-69	943 502 (12.10)	504 806 (10.07)	230 581 (14.91)	76 686 (10.49)	55 110 (27.79)	48 593 (28.21)	27 726 (20.51)
70-79	411 689 (5.28)	228 679 (4.56)	92 087 (5.96)	26 612 (3.64)	29 840 (15.05)	23 330 (13.54)	11 141 (8.24)
≥80	59 573 (0.76)	38 186 (0.76)	10 244 (0.66)	2344 (0.32)	5033 (2.54)	2737 (1.59)	1029 (0.76)
Male	4 058 470 (52.05)	2 040 555 (40.7)	1 102 651 (71.32)	611 600 (83.70)	95 510 (48.16)	106 579 (61.87)	101 575 (75.14)
Body mass index	23.57±3.21	22.17±2.41	25.54±2.23	27.99±3.03	22.73±2.29	25.37±2.27	27.95±3.22
<18.5	309 619 (3.97)	300 951 (6)	1379 (0.09)	235 (0.03)	6675 (3.37)	297 (0.17)	82 (0.06)
18.5-22.9	3 169 779 (40.66)	2 855 099 (56.94)	169 574 (10.97)	18 544 (2.54)	99 245 (50.04)	22 608 (13.12)	4709 (3.48)
23.0-24.9	1 902 839 (24.41)	1 235 636 (24.64)	460 369 (29.78)	78 245 (10.71)	60 212 (30.36)	52 296 (30.36)	16 081 (11.90)
25.0-29.9	2 156 883 (27.66)	616 277 (12.29)	863 366 (55.84)	470 029 (64.32)	31 927 (16.10)	92 125 (53.48)	83 159 (61.52)
≥30.0	257 643 (3.30)	6271 (0.13)	51 347 (3.32)	163 678 (22.40)	263 (0.13)	4931 (2.86)	31 153 (23.04)
Waist circumference, cm	79.54±9.03	75.26±6.96	85.75±5.32	91.98±6.77	78.78±6.23	86.21±5.55	92.72±7.21
Smoking status							
Never	4 861 868 (62.36)	3 546 339 (70.73)	756 908 (48.96)	269 372 (36.86)	132 366 (66.74)	96 803 (56.20)	60 080 (44.44)
Former	1 026 023 (13.16)	505 882 (10.09)	288 054 (18.63)	144 674 (19.80)	28 047 (14.14)	32 073 (18.62)	27 293 (20.19)
Current	1 908 872 (24.48)	962 013 (19.19)	501 073 (32.41)	316 685 (43.34)	37 909 (19.11)	43 381 (25.18)	47 811 (35.37)
Mild drinker	3 580 521 (45.92)	2 078 837 (41.46)	823 292 (53.25)	469 766 (64.29)	63 128 (31.83)	71 133 (41.29)	74 365 (55.01)
Regular exercise	1 375 132 (17.64)	860 257 (17.16)	283 495 (18.34)	121 718 (16.66)	46 744 (23.57)	37 614 (21.84)	25 304 (18.72)
Low income	1 718 725 (22.04)	1 173 477 (23.40)	296 780 (19.20)	133 560 (18.28)	46 553 (23.47)	38 600 (22.41)	29 755 (22.01)
Hypertension	1 784 001 (22.88)	758 171 (15.12)	475 757 (30.77)	278 841 (38.16)	90 076 (45.42)	97 989 (56.89)	83 167 (61.52)
Dyslipidemia	1 210 841 (15.53)	501 756 (10.01)	322 357 (20.85)	205 089 (28.07)	59 870 (30.19)	64 169 (37.25)	57 600 (42.61)
Diabetes duration ≥5 years	135 466 (1.74)	—	—	—	63 475 (32.01)	46 863 (27.21)	25 128 (18.59)
Insulin use	150 559 (1.93)	—	—	—	64 282 (32.41)	52 700 (30.59)	33 577 (24.84)
Oral antidiabetic drugs	274 454 (3.52)	—	—	—	115 353 (58.16)	96 631 (56.10)	62 470 (46.21)
Metformin	267 070 (3.43)	—	—	—	111 494 (56.22)	94 322 (54.76)	61 254 (45.31)
Sulfonylurea	257 015 (3.30)	—	—	—	106 433 (53.67)	90 990 (52.82)	59 592 (44.08)

(*Continued*)

Table 1 | Continued

Characteristics	Total (n=7 796 763)	Without type 2 diabetes mellitus			With type 2 diabetes mellitus		
		No NAFLD (n=5 014 234)	Grade 1 NAFLD (n=1 546 035)	Grade 2 NAFLD (n=730 731)	No NAFLD (n=198 322)	Grade 1 NAFLD (n=172 257)	Grade 2 NAFLD (n=135 184)
α-glucosidase inhibitor	121 631 (1.56)	—	—	—	53 417 (26.93)	42 013 (24.39)	26 201 (19.38)
Dipeptidyl peptidase 4 inhibitor	218 008 (2.80)	—	—	—	89 410 (45.08)	77 361 (44.91)	51 237 (37.90)
Thiazolidinedione	117 003 (1.50)	—	—	—	49 315 (24.87)	40 485 (23.50)	27 203 (20.12)
Meglitinide	36 133 (0.46)	—	—	—	16 843 (8.49)	12 121 (7.04)	7,169 (5.30)
No of oral antidiabetic drugs ≥3	237 501 (3.05)	—	—	—	98 082 (49.46)	84 010 (48.77)	55 409 (40.99)
Systolic blood pressure, mm Hg	121.63±14.84	118.49±14.06	125.85±14.08	129.22±14.31	125.79±15.61	129.56±15.32	132.33±15.56
Diastolic blood pressure, mm Hg	75.88±9.97	73.90±9.48	78.66±9.52	81.35±9.95	76.75±9.83	79.54±9.85	82.24±10.27
AST, IU/L	22.78 (22.77 to 22.78)	21.06 (21.05 to 21.06)	24.88 (24.87 to 24.89)	30.06 (30.03 to 30.09)	21.91 (21.88 to 21.94)	25.09 (25.05 to 25.14)	31.77 (31.69 to 31.85)
ALT, IU/L	20.55 (20.55 to 20.56)	17.03 (17.03 to 17.04)	26.22 (26.20 to 26.24)	37.65 (37.60 to 37.70)	19.98 (19.94 to 20.02)	26.82 (26.76 to 26.89)	37.95 (37.84 to 38.07)
GGT, IU/L	24.34 (24.33 to 24.35)	18.26 (18.25 to 18.27)	35.32 (35.29 to 35.35)	62.27 (62.17 to 62.37)	21.36 (21.32 to 21.41)	36.28 (36.18 to 36.38)	67.37 (67.11 to 67.63)
Fasting plasma glucose, mg/dL	95.73±21.36	90.76±10.85	94.55±11.69	96.56±12.28	142.83±46.90	147.03±47.05	154.89±49.86
Total cholesterol, mg/dL	195.13±36.47	189.00±34.18	204.81±35.96	213.33±37.96	191.02±38.80	201.32±40.64	211.58±43.24
Triglyceride, mg/dL	109.12 (109.08 to 109.17)	85.51 (85.47 to 85.54)	154.19 (154.09 to 154.29)	226.16 (225.91 to 226.41)	100.87 (100.67 to 101.07)	159.2 (158.87 to 159.53)	239.78 (239.13 to 240.43)
HDL cholesterol, mg/dL	56.25±27.82	58.84±26.02	52.27±31.17	49.53±29.69	55.48±27.95	51.45±28.48	49.33±26.67
LDL cholesterol, mg/dL	114.41±38.25	112.28±35.98	120.93±40.03	115.61±44.38	114.57±39.18	116.38±42.22	109.59±46.92
eGFR, mL/min/1.73 m^2	88.35±22.66	89.99±22.21	85.76±21.82	86.77±22.00	82.37±20.91	81.33±20.70	83.52±21.19

Data are presented as mean±standard deviation or geometric mean (95% confidence interval), or number (%). No NAFLD: fatty liver index<30; grade 1 NAFLD: 30≤fatty liver index<60; grade 2 NAFLD: fatty liver index≥60.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; eGFR=estimated glomerular filtration rate; GGT=γ-glutamyl transferase; HDL=high density lipoprotein; LDL=low density lipoprotein; NAFLD=non-alcoholic fatty liver disease.

those without T2DM (grade 1 NAFLD: 21.20%; grade 2 NAFLD: 10.02%).

During a median follow-up of 8.13 years, 34 255 people (6.77%) had cardiovascular disease and there were 42 372 deaths (8.38%) in patients with T2DM, whereas 163 657 people (2.24%) had cardiovascular disease and there were 197 645 deaths (2.71%) in those without T2DM (table 2). Incidence rates for cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death increased in

Table 2 | Risk of cardiovascular disease and all cause death according to non-alcoholic fatty liver disease

Disease and death by NAFLD	Number	Event	Person years	Incidence rate*	Hazard ratio (95% CI)		Five year absolute risk (95% CI)	Risk difference (95% CI)
					Unadjusted	Adjusted†		
Cardiovascular disease without T2DM								
No NAFLD	5 014 234	92 960	41 214 951.1	2.26	1 (reference)	1 (reference)	1.03 (1.02 to 1.04)	1 (reference)
Grade 1 NAFLD	1 546 035	48 244	12 612 022.5	3.83	1.70 (1.68 to 1.72)	1.23 (1.22 to 1.25)	1.23 (1.22 to 1.25)	0.21 (0.19 to 0.22)
Grade 2 NAFLD	730 731	22 453	5 951 160.3	3.77	1.68 (1.65 to 1.70)	1.44 (1.42 to 1.47)	1.42 (1.40 to 1.45)	0.40 (0.37 to 0.42)
Cardiovascular disease with T2DM								
No NAFLD	198 322	12 899	1 558 526.3	8.28	1 (reference)	1 (reference)	3.34 (3.27 to 3.41)	1 (reference)
Grade 1 NAFLD	172 257	12 456	1 355 111.2	9.19	1.11 (1.08 to 1.14)	1.10 (1.07 to 1.13)	3.94 (3.87 to 4.02)	0.61 (0.51 to 0.70)
Grade 2 NAFLD	135 184	8900	1 066 899.4	8.34	1.01 (0.98 to 1.04)	1.25 (1.22 to 1.29)	4.66 (4.54 to 4.78)	1.32 (1.17 to 1.47)
Myocardial infarction without T2DM								
No NAFLD	5 014 234	40 913	41 385 047.1	0.99	1 (reference)	1 (reference)	0.40 (0.40 to 0.41)	1 (reference)
Grade 1 NAFLD	1 546 035	22 073	12 701 919.7	1.74	1.76 (1.73 to 1.79)	1.27 (1.24 to 1.29)	0.50 (0.49 to 0.51)	0.10 (0.09 to 0.11)
Grade 2 NAFLD	730 731	11 075	5 990 134.5	1.85	1.88 (1.84 to 1.92)	1.52 (1.48 to 1.57)	0.60 (0.58 to 0.61)	0.19 (0.18 to 0.21)

(*Continued*)

Table 2 | Continued

Disease and death by NAFLD	Number	Event	Person years	Incidence rate*	Hazard ratio (95% CI)		Five year absolute risk (95% CI)	Risk difference (95% CI)
					Unadjusted	Adjusted†		
Myocardial infarction with T2DM								
No NAFLD	198 322	5397	1 583 174.8	3.41	1 (reference)	1 (reference)	1.29 (1.24 to 1.33)	1 (reference)
Grade 1 NAFLD	172 257	5236	1 379 825.8	3.79	1.11 (1.07 to 1.16)	1.07 (1.03 to 1.12)	1.49 (1.44 to 1.53)	0.20 (0.14 to 0.26)
Grade 2 NAFLD	135 184	3840	1 084 404.2	3.54	1.04 (1.00 to 1.09)	1.20 (1.15 to 1.25)	1.73 (1.65 to 1.80)	0.44 (0.35 to 0.53)
Ischaemic stroke without T2DM								
No NAFLD	5 014 234	55 611	41 323 432.0	1.35	1 (reference)	1 (reference)	0.65 (0.64 to 0.66)	1 (reference)
Grade 1 NAFLD	1 546 035	28 163	12 675 882.6	2.22	1.65 (1.63 to 1.68)	1.21 (1.19 to 1.24)	0.77 (0.76 to 0.78)	0.12 (0.11 to 0.13)
Grade 2 NAFLD	730 731	12 242	5 984 307.2	2.05	1.52 (1.49 to 1.55)	1.39 (1.36 to 1.42)	0.87 (0.85 to 0.89)	0.22 (0.20 to 0.24)
Ischaemic stroke with T2DM								
No NAFLD	198 322	8283	1 572 058.3	5.27	1 (reference)	1 (reference)	2.18 (2.13 to 2.24)	1 (reference)
Grade 1 NAFLD	172 257	7937	1 369 675.0	5.79	1.10 (1.07 to 1.13)	1.12 (1.08 to 1.15)	2.63 (2.56 to 2.69)	0.44 (0.36 to 0.52)
Grade 2 NAFLD	135 184	5556	1 077 814.5	5.15	0.98 (0.95 to 1.01)	1.30 (1.25 to 1.35)	3.16 (3.06 to 3.27)	0.98 (0.85 to 1.10)
All cause death without T2DM								
No NAFLD	5 014 234	125 920	41 500 456.8	3.03	1 (reference)	1 (reference)	1.25 (1.24 to 1.26)	1 (reference)
Grade 1 NAFLD	1 546 035	49 862	12 769 900.0	3.90	1.29 (1.27 to 1.30)	1.22 (1.21 to 1.24)	1.50 (1.48 to 1.51)	0.25 (0.23 to 0.26)
Grade 2 NAFLD	730 731	21 863	6 025 139.8	3.63	1.20 (1.18 to 1.22)	1.75 (1.72 to 1.78)	2.09 (2.06 to 2.12)	0.84 (0.81 to 0.87)
All cause death with T2DM								
No NAFLD	198 322	18 597	1 598 077.3	11.64	1 (reference)	1 (reference)	3.68 (3.61 to 3.74)	1 (reference)
Grade 1 NAFLD	172 257	14 155	13,95 864.0	10.14	0.87 (0.85 to 0.89)	1.14 (1.12 to 1.17)	4.25 (4.18 to 4.33)	0.58 (0.49 to 0.67)
Grade 2 NAFLD	135 184	9620	1 096 381.8	8.77	0.76 (0.74 to 0.77)	1.61 (1.57 to 1.65)	5.91 (5.78 to 6.05)	2.24 (2.08 to 2.39)

No NAFLD: fatty liver index<30; grade 1 NAFLD: 30≤fatty liver index<60; grade 2 NAFLD: fatty liver index≥60.
95% CI=95% confidence interval; NAFLD=non-alcoholic fatty liver disease; T2DM=type 2 diabetes mellitus.
*Incidence per 1000 person years.
†Adjusted for age, sex, smoking status, alcohol consumption, physical activity, low income, hypertension, dyslipidemia, body mass index, diabetes mellitus, and estimated glomerular filtration rate.

the order of no NAFLD, grade 1 NAFLD, and grade 2 NAFLD, and the incidence rates in patients with T2DM were higher than those in patients without T2DM (table 2, supplementary table S3). The hazard ratios for cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death were higher in the order of grade 1 NAFLD and grade 2 NAFLD compared with those in the no NAFLD group in patients with and without T2DM. Furthermore, the five year absolute risk for cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death increased in the order of no NAFLD, grade 1 NAFLD, and grade 2 NAFLD in patients without and with T2DM. In particular, patients with T2DM without NAFLD had a higher five year absolute risk for cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death than patients without T2DM with grade 2 NAFLD. Risk differences for cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death between no NAFLD and grade 2 NAFLD were higher than those between no NAFLD and grade 1 NAFLD. Additionally, risk differences for cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death between no NAFLD and grade 1 or grade 2 NAFLD were higher in patients with T2DM than in those without T2DM.

Kaplan-Meier survival curves showed that NAFLD was associated with a higher risk of cardiovascular disease (fig 1), myocardial infarction (fig 2), ischaemic stroke (fig 3), and all cause death (fig 4) in patients with and without T2DM (all P<0.001). Patients with grade 2 NAFLD had the highest risk of cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death, followed by those with grade 1 NAFLD.

The incidence rate of cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death increased in the order of no NAFLD, grade 1 NAFLD, and grade 2 NAFLD across all age groups, and increased with age (table 3). These rates were also higher in patients with T2DM than in those without T2DM. In the 20-29 year age group, the incidence rate of cardiovascular disease for patients with T2DM and no NAFLD was 0.40 per 1000 person years, but the rate was 23.25 per 1000 person years in the ≥70 year age group for patients with T2DM and grade 2 NAFLD. The hazard ratios for cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death were higher in the order of grade 1 NAFLD and grade 2 NAFLD compared with the hazard ratios for the no NAFLD group in all age groups.

The five year absolute risk for cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause

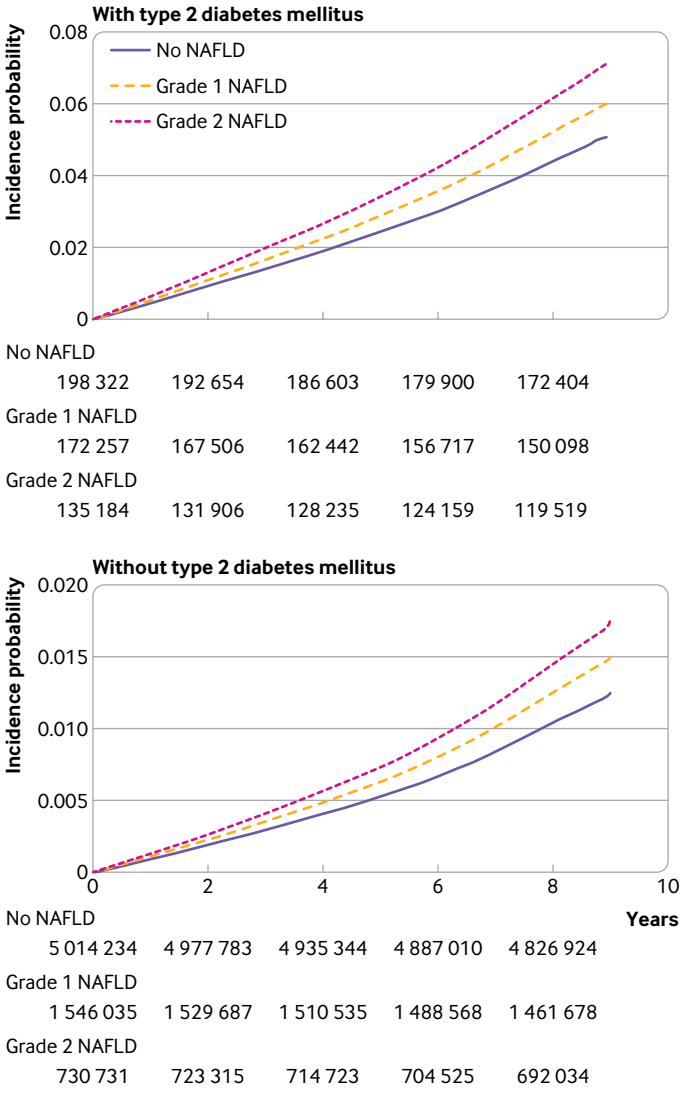

Fig 1 | Kaplan-Meier survival curve for cardiovascular disease according to the presence of non-alcoholic fatty liver disease (NAFLD) in patients with and without type 2 diabetes mellitus after adjusting for age, sex, smoking status, alcohol consumption, physical activity, low income, hypertension, dyslipidemia, body mass index, diabetes mellitus, and estimated glomerular filtration rate (all P<0.001). Numbers at risk presented below graphs

death increased in the order of no NAFLD, grade 1 NAFLD, and grade 2 NAFLD across all age groups, and increased with age. The risk was also higher in patients with T2DM than in those without T2DM. Risk differences for cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death between no NAFLD and grade 2 NAFLD were higher than those between no NAFLD and grade 1 NAFLD in all age groups, and increased with age. Risk differences for cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death between no NAFLD and grade 1 or grade 2 NAFLD were higher in patients with T2DM in all age groups compared with those without T2DM.

Subgroup analysis was performed for the following categories: sex, smoking status, abdominal obesity, aspartate aminotransferase or alanine aminotransferase, income, alcohol consumption, regular exercise, obesity, hypertension, dyslipidemia, chronic kidney disease, or γ-glutamyl transferase (supplementary figure S2). Across all subsets of patients with and without T2DM, NAFLD was associated with a higher risk of cardiovascular disease (supplementary figure S2A and S2B), myocardial infarction (supplementary figure S2C and S2D), ischaemic stroke (supplementary figure S2E and 2F), and all cause death (supplementary figure S2G and S2H). Hazard ratios for cardiovascular disease, myocardial infarction, ischaemic stroke, and all cause death for the grade 2 NAFLD group were mostly higher than those for the grade 1 NAFLD group, although the risks in both groups were higher than those for patients without NAFLD. Collinearity analysis showed no collinearity among the variables (supplementary table S4).

Discussion

This nationwide, population based, longitudinal cohort study showed that NAFLD in patients with T2DM was associated with a higher risk of cardiovascular disease and all cause death. The risk of cardiovascular disease and all cause death in patients with T2DM appears to be increased even in those with grade 1 NAFLD, which is a relatively mild degree of fatty liver. The grade 2 NAFLD group had a higher risk of cardiovascular disease and all cause death than patients in the no NAFLD group and those in the grade 1 NAFLD group. The five year absolute risk for cardiovascular disease and all cause death increased in the order of no NAFLD, grade 1 NAFLD, and grade 2 NAFLD in patients without and with T2DM, but it was higher in those with T2DM than in those without T2DM. Risk differences for cardiovascular disease and all cause death between no NAFLD and grade 2 NAFLD were higher than those between no NAFLD and grade 1 NAFLD, and they were also higher in patients with T2DM than in those without T2DM. This large study used real world data obtained from a national database to examine the risk of NAFLD for cardiovascular disease and all cause death in patients with T2DM.

Comparison with other studies

NAFLD is an underappreciated risk factor for atherosclerotic cardiovascular disease.[23 24] In a matched cohort study that enrolled 120 795 adults with NAFLD or non-alcoholic hepatic steatosis, the diagnosis of NAFLD did not appear to be associated with acute myocardial infarction or stroke risk after adjusting for established cardiovascular risk factors including T2DM.[25] However, a systematic review and meta-analysis of 26 observational studies with 85 395 participants showed that patients with NAFLD had a higher risk of subclinical atherosclerosis than those in the non-NAFLD group (odds ratio 1.60, 95% confidence interval 1.45 to 1.78).[26] Another meta-analysis of 16 observational studies including 34 043 participants and a median follow-up of 6.9 years showed that NAFLD is associated with increased odds of fatal or non-fatal cardiovascular

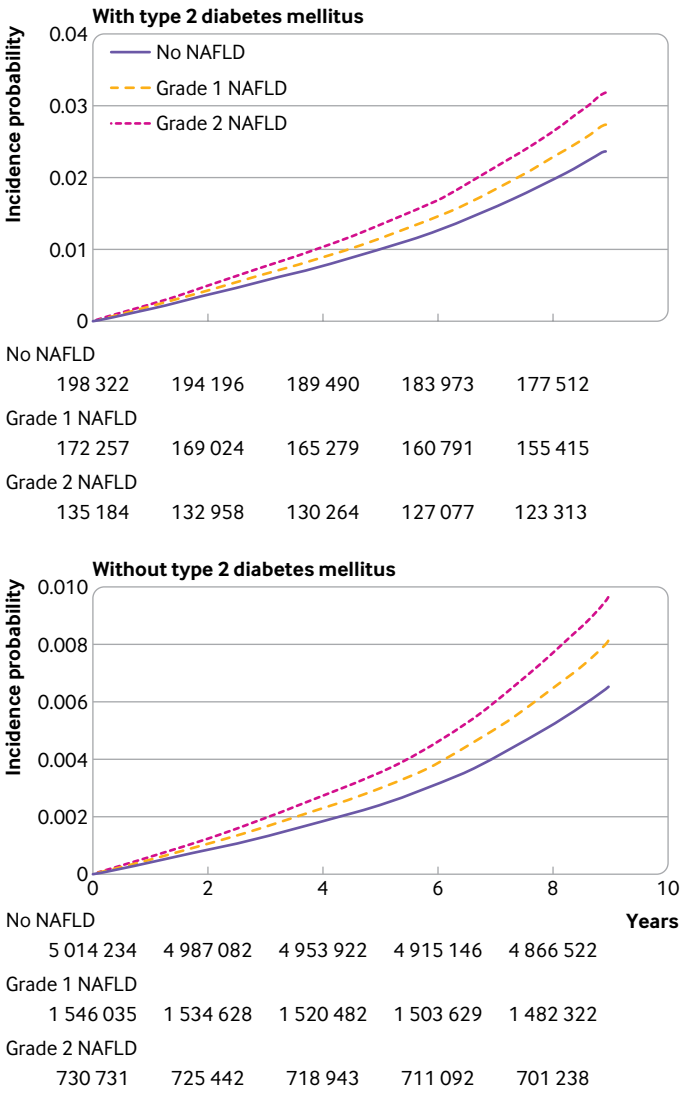

Fig 2 | Kaplan-Meier survival curve for myocardial infarction according to the presence of non-alcoholic fatty liver disease (NAFLD) in patients with and without type 2 diabetes mellitus after adjusting for age, sex, smoking status, alcohol consumption, physical activity, low income, hypertension, dyslipidemia, body mass index, diabetes mellitus, and estimated glomerular filtration rate (all P<0.001). Numbers at risk presented below graphs

disease events (random effects odds ratio 1.64, 95% confidence interval 1.26 to 2.13).[27] Additionally, NAFLD has been associated with an increased long term risk of fatal or non-fatal cardiovascular disease events in a meta-analysis of 36 longitudinal studies with aggregate data on 5 802 226 middle aged participants.[13]

Because T2DM is a well known risk factor for cardiovascular disease, patients with T2DM and NAFLD might be at greater risk of cardiovascular disease than those without these diseases. However, few studies have focused on people with T2DM, and the results are inconsistent. One study of 300 outpatients with T2DM from a tertiary care teaching hospital in India found no correlation between NAFLD and cardiovascular disease.[11] In contrast, a prospective case-control study of 2103 patients with T2DM without cardiovascular disease found that NAFLD was associated with an increased risk of cardiovascular disease during a five year follow-up after adjusting for other cardiovascular risk factors.[20] Another retrospective cohort study of 134 368 patients with T2DM from diabetes registry in Scotland found that patients with NAFLD had increased risk of cardiovascular disease and mortality compared with those without NAFLD during 4.5 years of follow-up.[21] In our study, we evaluated more than 7.7 million people including half a million patients with T2DM for a median of 8.13 years of follow-up. We were able to show an association between NAFLD and cardiovascular disease or all cause death in patients with T2DM.

Most studies that have investigated NAFLD and cardiovascular disease in patients with T2DM have evaluated hepatic steatosis using ultrasonography. Although it is a non-invasive and widely used procedure, ultrasonography is limited by substantial intraobserver and interobserver variability, can be unreliable with mild degrees of steatosis, and is not suitable for large scale population studies.[28] We used the fatty liver index instead of ultrasound, which is a simple and accurate surrogate marker of hepatic steatosis that has been validated in many studies.[22 29 30] Therefore, we were able to evaluate the association between NAFLD and cardiovascular disease in a large nationwide population of more than 7.7 million people. In Western populations, fatty liver index≥60 accurately identified the presence of hepatic steatosis.[22] When this cut-off value was applied to an Asian population, although the accuracy was similar (area under the curve 0.87), the Youden index decreased to 23-27%.[31] A study has reported that the optimal cut-off value of the fatty liver index to detect fatty liver with ultrasonography has been validated at ≥30 in the general population of Korea, with an area under the receiver operating characteristic curve of 0.82 (95% confidence interval 0.81 to 0.84).[32] In middle aged to elderly Chinese participants, the cut-off value of fatty liver index≥30 has presented a maximum Youden's index of 0.51 and achieved a high sensitivity of 79.9% and a specificity of 71.5%.[30]

The grade 1 NAFLD group had been associated with a higher risk of ischaemic stroke than the no NAFLD group in those with new onset T2DM.[33] Similarly, another study found that grade 1 and grade 2 fatty liver groups had higher risks of hepatocellular carcinoma and mortality than the no fatty liver group in those with chronic viral hepatitis.[34] In this study, the risk of cardiovascular disease and all cause death in patients with T2DM appears to be higher in those with grade 1 NAFLD, which is a relatively mild degree of fatty liver. This result shows that even mild NAFLD, which might not be detected by ultrasound, in patients with T2DM was associated with a higher risk of cardiovascular disease and all cause death. These findings suggest that mild NAFLD should be evaluated and managed to reduce the risk of cardiovascular disease or all cause death in patients with T2DM.

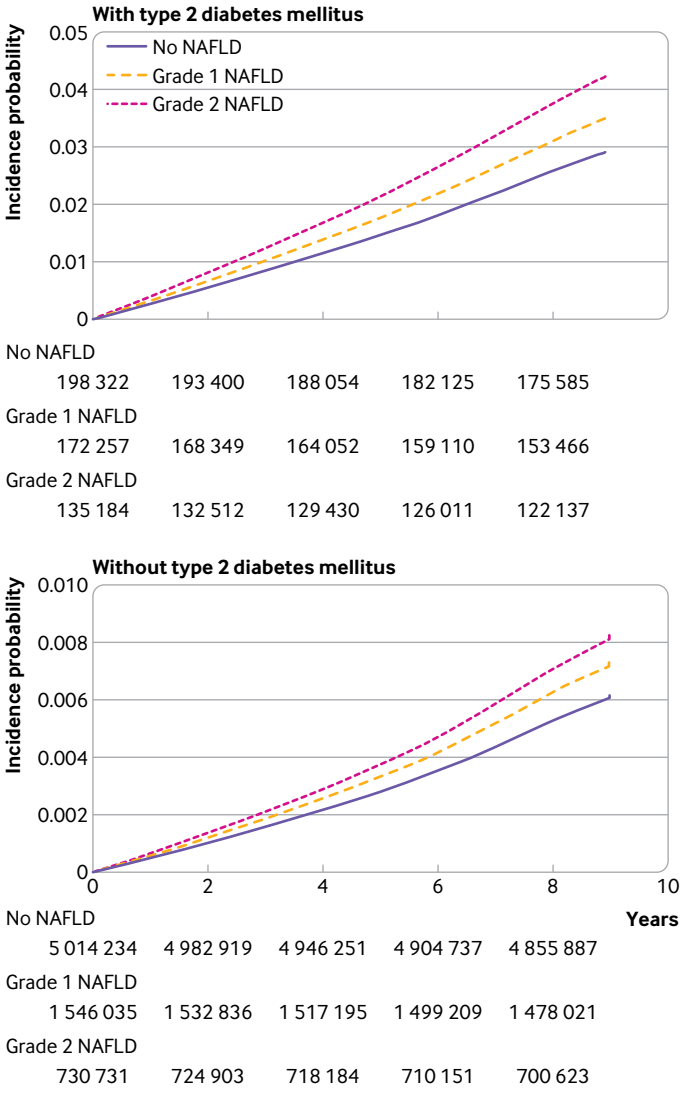

Fig 3 | Kaplan-Meier survival curve for ischaemic stroke according to the presence of non-alcoholic fatty liver disease (NAFLD) in patients with and without type 2 diabetes mellitus after adjusting for age, sex, smoking status, alcohol consumption, physical activity, low income, hypertension, dyslipidemia, body mass index, diabetes mellitus, and estimated glomerular filtration rate (all P<0.001). Numbers at risk presented below graphs

According to a previous study, the prevalence of fatty liver disease was highest in young patients (20-39 years) with T2DM compared with middle aged or older T2DM groups; there was also a steep increase in fatty liver disease in young patients with T2DM from 2009 to 2017.[2] Another study in a general population of people aged 20-39 years showed that NAFLD was associated with a higher risk of myocardial infarction (hazard ratio 1.69, 95% confidence interval 1.61 to 1.77).[35] A study of the Swedish National Diabetes Registry found that patients with T2DM detected at ≤40 years had an increased risk of myocardial infarction (hazard ratio 3.41, 95% confidence interval 2.88 to 4.04) compared with those without T2DM.[36] However, studies evaluating the risk of cardiovascular disease in young patients with T2DM and NAFLD have been lacking. In this study, although the incidence rate and absolute risk for cardiovascular disease in younger patients with T2DM were not higher than those for older age groups, the five year absolute risk for cardiovascular disease was higher in young patients with T2DM and grade 1 or grade 2 NAFLD than in those without NAFLD. Considering the recent increase in young patients with T2DM and NAFLD, preventative measures are needed to reduce the risk of cardiovascular disease.

Potential mechanisms for development of cardiovascular disease in patients with T2DM and NAFLD

The mechanisms linking NAFLD with cardiovascular disease in patients with T2DM are not clear. However, there are several potential pathophysiological pathways. NAFLD and T2DM create systemic, low grade inflammatory states that might promote atherosclerosis by secreting multiple cytokines and acute phase proteins.[37] Additionally, NAFLD and T2DM are proatherogenic conditions that result from increased levels of very low density lipoproteins and small, dense particles of low density lipoprotein cholesterol.[38] Prothrombotic conditions caused by increased platelet reactivity, higher levels of procoagulant drugs, and lower concentrations of endogenous anticoagulants might influence the development of cardiovascular disease in patients with T2DM and NAFLD.[39] NAFLD has a deleterious effect on glycaemic control in patients with T2DM; hyperglycaemia could account for the increased risk of cardiovascular disease in patients with T2DM and NAFLD.[40] Finally, because patients with T2DM and NAFLD tend to have a less healthy lifestyle, they are susceptible to unfavourable metabolic profiles that increase the risk of cardiovascular disease.

Limitations of this study

There are several limitations that should be considered. NAFLD was defined by the fatty liver index because liver biopsy or ultrasonography are not suitable for large scale epidemiologic studies. However, this index is a well known, non-invasive biomarker for predicting hepatic steatosis and has been validated in the Korean population[41] and worldwide.[22] We were unable to analyse haemoglobin A_{1c} variability or changes in diabetes drugs during the follow-up period owing to database limitations.

Although the results of this study might not be generalisable to other ethnicities because of the Korean study population, we believe that the findings are important for Asians who have similar eating habits and body composition to Koreans. However, generalising the results of this study to Western populations with different eating habits, body composition, and genetic factors might require caution. Finally, we could not evaluate hepatic fibrosis, which might influence the risk of cardiovascular disease in patients with T2DM and NAFLD. Overall, however, our study findings are valuable because they show the association between NAFLD and cardiovascular disease risk in patients with T2DM.

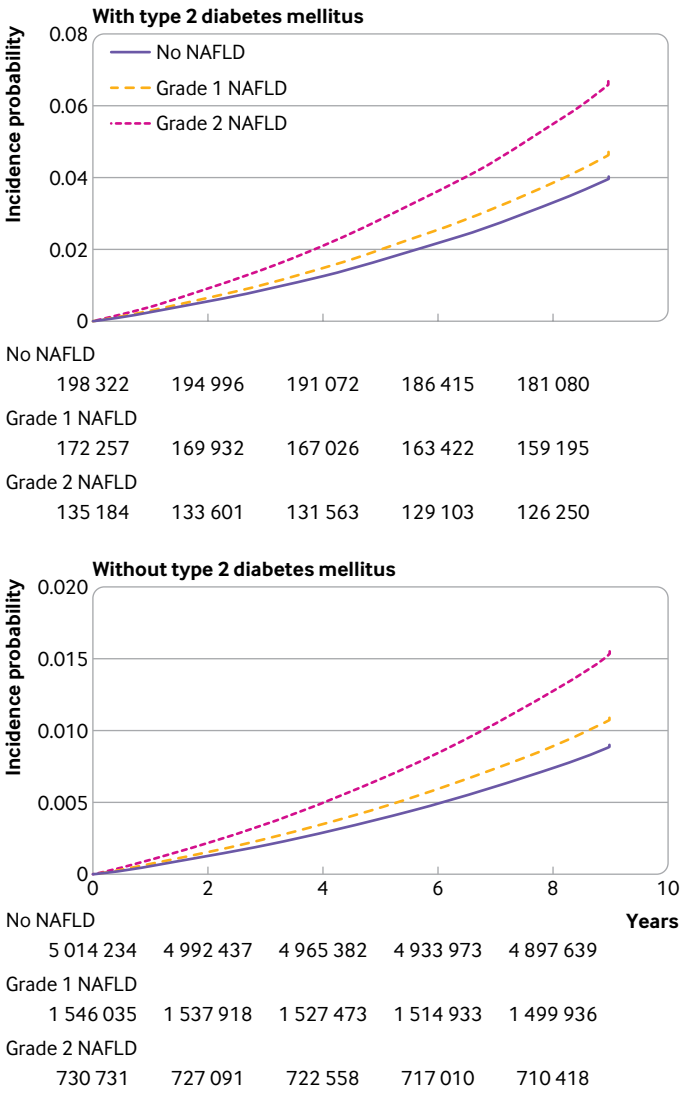

Fig 4 | Kaplan-Meier survival curve for all cause death according to the presence of non-alcoholic fatty liver disease (NAFLD) in patients with and without type 2 diabetes mellitus after adjusting for age, sex, smoking status, alcohol consumption, physical activity, low income, hypertension, dyslipidemia, body mass index, diabetes mellitus, and estimated glomerular filtration rate (all P<0.001). Numbers at risk presented below graphs

Conclusions

NAFLD in patients with T2DM seems to be associated with a higher risk of cardiovascular disease and all cause death even in patients with mild NAFLD. Risk differences for cardiovascular disease and all cause death between no NAFLD and grade 1 or grade 2 NAFLD were higher in patients with T2DM than in those without T2DM. This study suggests that NAFLD screening and prevention are required to reduce the risk of cardiovascular disease and all cause death in patients with T2DM.

Contributors: KH and C-YP contributed equally as corresponding authors. K-SK, KH, and C-YP contributed to the conception and design of the study. All authors carried out acquisition, analysis, or interpretation of data. K-SK wrote the first draft. All authors read and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. KH and C-YP are the guarantors. The corresponding authors attest that all listed authors meet authorship criteria and that no authors meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the institutional review board of Soongsil University (SSU-202003-HR-201-01). The requirement for informed consent was waived by the institutional review board because the dataset was deidentified to protect personal information.

Data sharing: Additional data are available through approval and oversight by the Korean National Health Insurance Service.

The lead authors (KH and C-YP) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of this work will be disseminated to the public through press releases, presentations at conferences oriented towards clinicians that manage patients with type 2 diabetes mellitus, and plain language summaries posted on websites and social media.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73-84. doi:10.1002/hep.28431
2 Han E, Han KD, Lee YH, et al. Fatty Liver & Diabetes Statistics in Korea: Nationwide Data 2009 to 2017. *Diabetes Metab J* 2023;47:347-55. doi:10.4093/dmj.2022.0444
3 Birkenfeld AL, Shulman GI. Nonalcoholic fatty liver disease, hepatic insulin resistance, and type 2 diabetes. *Hepatology* 2014;59:713-23. doi:10.1002/hep.26672
4 Kim KS, Hong S, Ahn HY, Park CY. Triglyceride and glucose index is a simple and easy-to-calculate marker associated with nonalcoholic fatty liver disease. *Obesity (Silver Spring)* 2022;30:1279-88. doi:10.1002/oby.23438
5 Kim KS, Hong S, Ahn HY, Park CY. Metabolic dysfunction-associated fatty liver disease and mortality: a population-based cohort study. *Diabetes Metab J* 2023;47:220-31. doi:10.4093/dmj.2021.0327
6 Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2018;15:11-20. doi:10.1038/nrgastro.2017.109
7 Muzurović E, Mikhailidis DP, Mantzoros C. Non-alcoholic fatty liver disease, insulin resistance, metabolic syndrome and their association with vascular risk. *Metabolism* 2021;119:154770. doi:10.1016/j.metabol.2021.154770
8 Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2021;18:223-38. doi:10.1038/s41575-020-00381-6
9 Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. *Lancet Diabetes Endocrinol* 2022;10:284-96. doi:10.1016/S2213-8587(22)00003-1
10 Caussy C, Aubin A, Loomba R. The relationship between type 2 diabetes, nafld, and cardiovascular risk. *Curr Diab Rep* 2021;21:15. doi:10.1007/s11892-021-01383-7
11 Vanjiappan S, Hamide A, Ananthakrishnan R, Periyasamy SG, Mehalingam V. Nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and its association with cardiovascular disease. *Diabetes Metab Syndr* 2018;12:479-82. doi:10.1016/j.dsx.2018.01.001
12 Zhou YY, Zhou XD, Wu SJ, et al. Synergistic increase in cardiovascular risk in diabetes mellitus with nonalcoholic fatty liver disease: a meta-analysis. *Eur J Gastroenterol Hepatol* 2018;30:631-6. doi:10.1097/MEG.0000000000001075

Table 3 | Risk of cardiovascular disease and all cause death according to non-alcoholic fatty liver disease stratified by age

Disease and death by age	Without type 2 diabetes mellitus				With type 2 diabetes mellitus			
	Incidence rate*	Hazard ratio† (95% CI)	Five year absolute risk (95% CI)	Risk difference (95% CI)	Incidence rate*	Hazard ratio† (95% CI)	Five year absolute risk (95% CI)	Risk difference (95% CI)
Cardiovascular disease								
20-29 years								
No NAFLD	0.26	1 (reference)	0.09 (0.08 to 0.09)	1 (reference)	0.40	1 (reference)	0.11 (0.03 to 0.19)	1 (reference)
Grade 1 NAFLD	0.41	1.27 (1.14 to 1.42)	0.09 (0.08 to 0.11)	0.01 (−0.01 to 0.02)	0.60	1.63 (0.70 to 3.82)	0.15 (0.03 to 0.27)	0.04 (−0.09 to 0.17)
Grade 2 NAFLD	0.76	2.18 (1.94 to 2.44)	0.13 (0.11 to 0.15)	0.04 (0.02 to 0.06)	1.21	3.53 (1.86 to 6.68)	0.24 (0.05 to 0.43)	0.13 (−0.07 to 0.34)
30-39 years								
No NAFLD	0.47	1 (reference)	0.18 (0.17 to 0.19)	1 (reference)	1.10	1 (reference)	0.56 (0.43 to 0.70)	1 (reference)
Grade 1 NAFLD	0.80	1.42 (1.35 to 1.50)	0.23 (0.21 to 0.24)	0.05 (0.03 to 0.06)	1.60	1.50 (1.16 to 1.94)	0.65 (0.53 to 0.78)	0.09 (−0.07 to 0.25)
Grade 2 NAFLD	1.30	2.12 (2.01 to 2.24)	0.28 (0.26 to 0.30)	0.10 (0.08 to 0.12)	2.57	2.57 (2.07 to 3.20)	0.82 (0.70 to 0.95)	0.26 (0.07 to 0.45)
40-49 years								
No NAFLD	1.17	1 (reference)	0.49 (0.48 to 0.50)	1 (reference)	3.02	1 (reference)	1.36 (1.25 to 1.48)	1 (reference)
Grade 1 NAFLD	2.12	1.45 (1.40 to 1.49)	0.64 (0.62 to 0.65)	0.14 (0.12 to 0.16)	3.87	1.26 (1.15 to 1.38)	1.58 (1.47 to 1.69)	0.22 (0.08 to 0.36)
Grade 2 NAFLD	2.72	1.67 (1.61 to 1.73)	0.65 (0.63 to 0.68)	0.16 (0.13 to 0.19)	4.45	1.48 (1.35 to 1.62)	1.72 (1.59 to 1.85)	0.35 (0.17 to 0.54)
50-59 years								
No NAFLD	2.49	1 (reference)	1.10 (1.08 to 1.12)	1 (reference)	5.30	1 (reference)	2.35 (2.23 to 2.47)	1 (reference)
Grade 1 NAFLD	3.93	1.35 (1.32 to 1.38)	1.35 (1.32 to 1.38)	0.25 (0.22 to 0.29)	6.31	1.20 (1.13 to 1.27)	2.70 (2.58 to 2.82)	0.35 (0.20 to 0.50)
Grade 2 NAFLD	4.81	1.49 (1.45 to 1.54)	1.41 (1.36 to 1.46)	0.31 (0.26 to 0.36)	7.34	1.44 (1.35 to 1.53)	3.13 (2.97 to 3.29)	0.78 (0.57 to 0.99)
60-69 years								
No NAFLD	5.89	1 (reference)	2.47 (2.43 to 2.51)	1 (reference)	10.20	1 (reference)	4.16 (4.01 to 4.31)	1 (reference)
Grade 1 NAFLD	7.63	1.18 (1.16 to 1.21)	2.97 (2.91 to 3.03)	0.50 (0.43 to 0.57)	11.73	1.20 (1.15 to 1.25)	5.06 (4.89 to 5.23)	0.90 (0.69 to 1.11)
Grade 2 NAFLD	9.02	1.31 (1.27 to 1.35)	3.33 (3.22 to 3.44)	0.86 (0.74 to 0.98)	13.10	1.40 (1.33 to 1.48)	6.00 (5.72 to 6.28)	1.84 (1.52 to 2.16)
≥70 years								
No NAFLD	14.12	1 (reference)	6.32 (6.23 to 6.41)	1 (reference)	19.84	1 (reference)	8.58 (8.29 to 8.86)	1 (reference)
Grade 1 NAFLD	15.76	1.03 (1.00 to 1.05)	7.27 (7.13 to 7.42)	0.95 (0.79 to 1.12)	21.59	1.15 (1.10 to 1.20)	10.0 (9.66 to 10.3)	1.42 (1.00 to 1.84)
Grade 2 NAFLD	17.25	1.07 (1.03 to 1.11)	8.15 (7.86 to 8.44)	1.83 (1.53 to 2.14)	23.25	1.33 (1.25 to 1.41)	11.6 (11.0 to 12.2)	3.03 (2.36 to 3.71)
Myocardial infarction								
20-29 years								
No NAFLD	0.16	1 (reference)	0.05 (0.05 to 0.06)	1 (reference)	0.33	1 (reference)	0.11 (0.01 to 0.21)	1 (reference)
Grade 1 NAFLD	0.27	1.24 (1.08 to 1.43)	0.05 (0.05 to 0.06)	0.00 (−0.01 to 0.01)	0.15	0.49 (0.11 to 2.15)	0.04 (0.00 to 0.09)	−0.07 (−0.18 to 0.03)
Grade 2 NAFLD	0.46	1.99 (1.72 to 2.30)	0.07 (0.06 to 0.09)	0.02 (0.01 to 0.04)	0.53	1.75 (0.77 to 4.00)	0.10 (0.00 to 0.21)	−0.01 (−0.16 to 0.14)
30-39 years								
No NAFLD	0.27	1 (reference)	0.09 (0.09 to 0.10)	1 (reference)	0.65	1 (reference)	0.29 (0.20 to 0.37)	1 (reference)
Grade 1 NAFLD	0.49	1.51 (1.41 to 1.61)	0.13 (0.12 to 0.14)	0.03 (0.02 to 0.04)	0.98	1.49 (1.07 to 2.07)	0.37 (0.27 to 0.46)	0.08 (−0.03 to 0.19)
Grade 2 NAFLD	0.82	2.28 (2.12 to 2.44)	0.17 (0.15 to 0.18)	0.07 (0.06 to 0.09)	1.65	2.62 (1.98 to 3.47)	0.54 (0.43 to 0.65)	0.26 (0.11 to 0.40)
40-49 years								
No NAFLD	0.61	1 (reference)	0.24 (0.23 to 0.25)	1 (reference)	1.51	1 (reference)	0.73 (0.64 to 0.82)	1 (reference)
Grade 1 NAFLD	1.17	1.48 (1.42 to 1.54)	0.31 (0.30 to 0.33)	0.07 (0.06 to 0.09)	1.93	1.23 (1.08 to 1.40)	0.76 (0.69 to 0.84)	0.03 (−0.07 to 0.14)
Grade 2 NAFLD	1.59	1.78 (1.70 to 1.87)	0.34 (0.32 to 0.36)	0.10 (0.08 to 0.12)	2.29	1.47 (1.29 to 1.67)	0.79 (0.71 to 0.87)	0.06 (−0.07 to 0.19)
50-59 years								
No NAFLD	1.17	1 (reference)	0.48 (0.46 to 0.49)	1 (reference)	2.34	1 (reference)	0.98 (0.90 to 1.06)	1 (reference)
Grade 1 NAFLD	1.95	1.41 (1.36 to 1.46)	0.60 (0.58 to 0.62)	0.12 (0.10 to 0.15)	2.98	1.27 (1.17 to 1.38)	1.19 (1.11 to 1.26)	0.21 (0.11 to 0.30)
Grade 2 NAFLD	2.39	1.55 (1.48 to 1.62)	0.62 (0.59 to 0.65)	0.14 (0.11 to 0.17)	3.29	1.43 (1.30 to 1.57)	1.29 (1.19 to 1.39)	0.31 (0.18 to 0.44)
60-69 years								
No NAFLD	2.38	1 (reference)	0.92 (0.90 to 0.95)	1 (reference)	4.07	1 (reference)	1.54 (1.45 to 1.63)	1 (reference)
Grade 1 NAFLD	3.11	1.18 (1.14 to 1.22)	1.11 (1.07 to 1.14)	0.18 (0.15 to 0.22)	4.56	1.15 (1.08 to 1.23)	1.78 (1.68 to 1.88)	0.24 (0.12 to 0.36)
Grade 2 NAFLD	3.72	1.32 (1.25 to 1.38)	1.25 (1.19 to 1.31)	0.33 (0.26 to 0.39)	5.15	1.35 (1.25 to 1.47)	2.09 (1.94 to 2.25)	0.55 (0.37 to 0.74)
≥70 years								
No NAFLD	5.15	1 (reference)	2.08 (2.03 to 2.13)	1 (reference)	7.51	1 (reference)	2.95 (2.78 to 3.11)	1 (reference)
Grade 1 NAFLD	5.84	1.01 (0.98 to 1.05)	2.53 (2.44 to 2.62)	0.45 (0.35 to 0.54)	7.88	1.08 (1.00 to 1.15)	3.40 (3.20 to 3.60)	0.45 (0.21 to 0.69)
Grade 2 NAFLD	6.31	1.04 (0.99 to 1.11)	2.95 (2.77 to 3.12)	0.87 (0.68 to 1.05)	7.90	1.13 (1.03 to 1.24)	3.79 (3.45 to 4.13)	0.84 (0.46 to 1.23)
Ischaemic stroke								
20-29 years								
No NAFLD	0.10	1 (reference)	0.04 (0.03 to 0.04)	1 (reference)	0.08	1 (reference)	0.02 (0.00 to 0.04)	1 (reference)
Grade 1 NAFLD	0.15	1.32 (1.10 to 1.58)	0.04 (0.03 to 0.05)	0.00 (0.00 to 0.01)	0.45	6.77 (1.69 to 27.05)	0.11 (0.00 to 0.23)	0.10 (−0.02 to 0.21)
Grade 2 NAFLD	0.30	2.44 (2.04 to 2.93)	0.06 (0.04 to 0.07)	0.02 (0.01 to 0.04)	0.68	11.34 (3.23 to 39.80)	0.16 (0.00 to 0.35)	0.14 (−0.05 to 0.34)
30-39 years								
No NAFLD	0.21	1 (reference)	0.09 (0.08 to 0.10)	1 (reference)	0.48	1 (reference)	0.32 (0.19 to 0.44)	1 (reference)
Grade 1 NAFLD	0.32	1.31 (1.21 to 1.43)	0.10 (0.09 to 0.11)	0.01 (0.00 to 0.02)	0.65	1.41 (0.96 to 2.09)	0.30 (0.20 to 0.39)	−0.02 (−0.15 to 0.11)
Grade 2 NAFLD	0.50	1.92 (1.77 to 2.09)	0.12 (0.11 to 0.13)	0.03 (0.02 to 0.04)	1.00	2.38 (1.71 to 3.32)	0.29 (0.22 to 0.36)	−0.03 (−0.17 to 0.12)
40-49 years								
No NAFLD	0.58	1 (reference)	0.26 (0.25 to 0.26)	1 (reference)	1.61	1 (reference)	0.67 (0.59 to 0.74)	1 (reference)
Grade 1 NAFLD	0.98	1.40 (1.35 to 1.47)	0.33 (0.32 to 0.34)	0.07 (0.06 to 0.09)	2.01	1.26 (1.11 to 1.43)	0.84 (0.76 to 0.92)	0.18 (0.08 to 0.28)
Grade 2 NAFLD	1.18	1.53 (1.45 to 1.61)	0.32 (0.30 to 0.34)	0.06 (0.04 to 0.09)	2.25	1.45 (1.29 to 1.64)	0.96 (0.86 to 1.06)	0.29 (0.16 to 0.43)

(*Continued*)

Table 3 | Continued

Disease and death by age	Without type 2 diabetes mellitus				With type 2 diabetes mellitus			
	Incidence rate*	Hazard ratio† (95% CI)	Five year absolute risk (95% CI)	Risk difference (95% CI)	Incidence rate*	Hazard ratio† (95% CI)	Five year absolute risk (95% CI)	Risk difference (95% CI)
50-59 years								
No NAFLD	1.37	1 (reference)	0.64 (0.62 to 0.65)	1 (reference)	3.15	1 (reference)	1.43 (1.34 to 1.52)	1 (reference)
Grade 1 NAFLD	2.07	1.31 (1.27 to 1.35)	0.77 (0.75 to 0.79)	0.14 (0.11 to 0.16)	3.53	1.15 (1.06 to 1.23)	1.59 (1.50 to 1.68)	0.16 (0.04 to 0.28)
Grade 2 NAFLD	2.52	1.46 (1.39 to 1.52)	0.82 (0.78 to 0.85)	0.18 (0.14 to 0.22)	4.27	1.44 (1.33 to 1.56)	1.95 (1.82 to 2.08)	0.52 (0.35 to 0.69)
60-69 years								
No NAFLD	3.68	1 (reference)	1.60 (1.57 to 1.64)	1 (reference)	6.62	1 (reference)	2.78 (2.66 to 2.91)	1 (reference)
Grade 1 NAFLD	4.74	1.19 (1.16 to 1.22)	1.94 (1.89 to 1.99)	0.33 (0.28 to 0.39)	7.68	1.23 (1.16 to 1.29)	3.49 (3.35 to 3.63)	0.71 (0.53 to 0.88)
Grade 2 NAFLD	5.61	1.33 (1.28 to 1.38)	2.19 (2.10 to 2.28)	0.58 (0.49 to 0.68)	8.62	1.45 (1.36 to 1.55)	4.22 (3.98 to 4.46)	1.43 (1.15 to 1.71)
≥70 years								
No NAFLD	9.56	1 (reference)	4.52 (4.45 to 4.60)	1 (reference)	13.20	1 (reference)	6.07 (5.82 to 6.31)	1 (reference)
Grade 1 NAFLD	10.59	1.05 (1.02 to 1.08)	5.11 (4.99 to 5.24)	0.59 (0.45 to 0.73)	14.64	1.20 (1.13 to 1.26)	7.16 (6.86 to 7.45)	1.09 (0.72 to 1.45)
Grade 2 NAFLD	11.71	1.11 (1.06 to 1.16)	5.67 (5.42 to 5.91)	1.14 (0.88 to 1.40)	16.33	1.46 (1.36 to 1.56)	8.56 (8.03 to 9.08)	2.49 (1.89 to 3.09)
All cause death								
20-29 years								
No NAFLD	0.33	1 (reference)	0.17 (0.16 to 0.18)	1 (reference)	0.60	1 (reference)	0.30 (0.13 to 0.47)	1 (reference)
Grade 1 NAFLD	0.45	1.49 (1.35 to 1.66)	0.17 (0.15 to 0.19)	0.00 (−0.02 to 0.02)	0.83	2.00 (0.98 to 4.08)	0.38 (0.14 to 0.63)	0.08 (−0.21 to 0.37)
Grade 2 NAFLD	0.62	2.74 (2.42 to 3.09)	0.22 (0.19 to 0.26)	0.05 (0.02 to 0.09)	0.79	2.88 (1.51 to 5.49)	0.36 (0.08 to 0.63)	0.05 (−0.31 to 0.41)
30-39 years								
No NAFLD	0.54	1 (reference)	0.25 (0.24 to 0.26)	1 (reference)	1.17	1 (reference)	0.45 (0.34 to 0.55)	1 (reference)
Grade 1 NAFLD	0.65	1.35 (1.27 to 1.42)	0.29 (0.27 to 0.30)	0.03 (0.02 to 0.05)	1.22	1.32 (1.01 to 1.73)	0.48 (0.37 to 0.58)	0.03 (−0.10 to 0.16)
Grade 2 NAFLD	0.82	2.10 (1.97 to 2.23)	0.36 (0.33 to 0.39)	0.11 (0.08 to 0.14)	1.56	2.37 (1.89 to 2.98)	0.67 (0.53 to 0.80)	0.22 (0.04 to 0.41)
40-49 years								
No NAFLD	0.97	1 (reference)	0.45 (0.44 to 0.46)	1 (reference)	2.38	1 (reference)	0.86 (0.78 to 0.95)	1 (reference)
Grade 1 NAFLD	1.43	1.43 (1.38 to 1.48)	0.59 (0.57 to 0.61)	0.15 (0.12 to 0.17)	2.53	1.22 (1.09 to 1.35)	1.10 (1.01 to 1.19)	0.23 (0.12 to 0.35)
Grade 2 NAFLD	1.77	1.98 (1.90 to 2.06)	0.75 (0.71 to 0.78)	0.30 (0.26 to 0.34)	3.18	1.85 (1.68 to 2.05)	1.71 (1.55 to 1.86)	0.84 (0.66 to 1.02)
50-59 years								
No NAFLD	2.11	1 (reference)	0.94 (0.92 to 0.96)	1 (reference)	4.74	1 (reference)	1.80 (1.71 to 1.90)	1 (reference)
Grade 1 NAFLD	2.85	1.40 (1.37 to 1.44)	1.20 (1.17 to 1.23)	0.26 (0.22 to 0.29)	4.84	1.19 (1.12 to 1.26)	2.10 (2.00 to 2.20)	0.30 (0.17 to 0.43)
Grade 2 NAFLD	3.99	2.12 (2.05 to 2.19)	1.69 (1.63 to 1.75)	0.75 (0.68 to 0.81)	6.05	1.76 (1.65 to 1.88)	3.06 (2.89 to 3.24)	1.26 (1.06 to 1.46)
60-69 years								
No NAFLD	6.71	1 (reference)	2.57 (2.53 to 2.61)	1 (reference)	11.38	1 (reference)	4.01 (3.87 to 4.14)	1 (reference)
Grade 1 NAFLD	7.24	1.28 (1.25 to 1.30)	3.17 (3.11 to 3.23)	0.60 (0.53 to 0.67)	11.20	1.21 (1.16 to 1.27)	4.72 (4.56 to 4.88)	0.72 (0.52 to 0.91)
Grade 2 NAFLD	9.37	1.83 (1.77 to 1.88)	4.41 (4.27 to 4.54)	1.84 (1.70 to 1.98)	13.36	1.73 (1.65 to 1.82)	6.53 (6.24 to 6.82)	2.52 (2.20 to 2.84)
≥70 years								
No NAFLD	24.01	1 (reference)	10.5 (10.4 to 10.6)	1 (reference)	32.97	1 (reference)	13.2 (12.9 to 13.5)	1 (reference)
Grade 1 NAFLD	21.76	1.09 (1.07 to 1.11)	12.1 (11.9 to 12.3)	1.67 (1.47 to 1.87)	29.77	1.13 (1.09 to 1.17)	14.7 (14.3 to 15.1)	1.55 (1.10 to 1.99)
Grade 2 NAFLD	24.77	1.40 (1.36 to 1.44)	15.8 (15.4 to 16.2)	5.34 (4.93 to 5.75)	33.98	1.53 (1.47 to 1.60)	19.3 (18.6 to 20.0)	6.15 (5.39 to 6.91)

No NAFLD: fatty liver index<30; grade 1 NAFLD: 30≤fatty liver index<60; grade 2 NAFLD: fatty liver index≥60.
95% CI=95% confidence interval; NAFLD=non-alcoholic fatty liver disease.
*Incidence per 1000 person years.
†Adjusted for age, sex, smoking status, alcohol consumption, physical activity, low income, hypertension, dyslipidemia, body mass index, diabetes mellitus, and estimated glomerular filtration rate.

13 Mantovani A, Csermely A, Petracca G, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2021;6:903-13. doi:10.1016/S2468-1253(21)00308-3
14 Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005;129:113-21. doi:10.1053/j.gastro.2005.04.014
15 Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. *J Hepatol* 2008;49:608-12. doi:10.1016/j.jhep.2008.06.018
16 Bae JH, Han KD, Ko SH, et al. Diabetes fact sheet in Korea 2021. *Diabetes Metab J* 2022;46:417-26. doi:10.4093/dmj.2022.0106
17 ElSayed NA, Aleppo G, Aroda VR, et al, on behalf of the American Diabetes Association. 10. Cardiovascular disease and risk management: standards of care in diabetes-2023. *Diabetes Care* 2023;46(Suppl 1):S158-90. doi:10.2337/dc23-S010
18 Lee BW, Lee YH, Park CY, et al, Korean Diabetes Association (KDA) Fatty Liver Research Group. Non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus: a position statement of the Fatty Liver Research Group of the Korean Diabetes Association. *Diabetes Metab J* 2020;44:382-401. doi:10.4093/dmj.2020.0010
19 Targher G, Bertolini L, Rodella S, et al. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. *Diabetes Care* 2007;30:2119-21. doi:10.2337/dc07-0349
20 Targher G, Bertolini L, Poli F, et al. Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. *Diabetes* 2005;54:3541-6. doi:10.2337/diabetes.54.12.3541
21 Wild SH, Walker JJ, Morling JR, et al, Scottish Diabetes Research Network Epidemiology Group. Cardiovascular disease, cancer, and mortality among people with type 2 diabetes and alcoholic or nonalcoholic fatty liver disease hospital admission. *Diabetes Care* 2018;41:341-7. doi:10.2337/dc17-1590
22 Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 2006;6:33. doi:10.1186/1471-230X-6-33
23 Kim KS, Lee BW, Kim YJ, Lee DH, Cha BS, Park CY. Nonalcoholic fatty liver disease and diabetes: part ii: treatment. *Diabetes Metab J* 2019;43:127-43. doi:10.4093/dmj.2019.0034
24 Cho Y, Lee YH. State-of-the-art overview of the pharmacological treatment of non-alcoholic steatohepatitis. *Endocrinol Metab (Seoul)* 2022;37:38-52. doi:10.3803/EnM.2022.102
25 Alexander M, Loomis AK, van der Lei J, et al. Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults. *BMJ* 2019;367:l5367. doi:10.1136/bmj.l5367
26 Zhou YY, Zhou XD, Wu SJ, et al. Nonalcoholic fatty liver disease contributes to subclinical atherosclerosis: A systematic review and meta-analysis. *Hepatol Commun* 2018;2:376-92. doi:10.1002/hep4.1155

27 Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: a meta-analysis. *J Hepatol* 2016;65:589-600. doi:10.1016/j.jhep.2016.05.013
28 Roldan-Valadez E, Favila R, Martínez-López M, Uribe M, Méndez-Sánchez N. Imaging techniques for assessing hepatic fat content in nonalcoholic fatty liver disease. *Ann Hepatol* 2008;7:212-20. doi:10.1016/S1665-2681(19)31850-2
29 Cuthbertson DJ, Weickert MO, Lythgoe D, et al. External validation of the fatty liver index and lipid accumulation product indices, using 1H-magnetic resonance spectroscopy, to identify hepatic steatosis in healthy controls and obese, insulin-resistant individuals. *Eur J Endocrinol* 2014;171:561-9. doi:10.1530/EJE-14-0112
30 Huang X, Xu M, Chen Y, et al. Validation of the fatty liver index for nonalcoholic fatty liver disease in middle-aged and elderly Chinese. *Medicine (Baltimore)* 2015;94:e1682. doi:10.1097/MD.0000000000001682
31 Lee YH, Bang H, Park YM, et al. Non-laboratory-based self-assessment screening score for non-alcoholic fatty liver disease: development, validation and comparison with other scores. *PLoS One* 2014;9:e107584. doi:10.1371/journal.pone.0107584
32 Cho EJ, Jung GC, Kwak MS, et al. Fatty liver index for predicting nonalcoholic fatty liver disease in an asymptomatic Korean population. *Diagnostics (Basel)* 2021;11:2233. doi:10.3390/diagnostics11122233
33 Park J, Kim G, Kim BS, et al. The associations of hepatic steatosis and fibrosis using fatty liver index and BARD score with cardiovascular outcomes and mortality in patients with new-onset type 2 diabetes: a nationwide cohort study. *Cardiovasc Diabetol* 2022;21:53. doi:10.1186/s12933-022-01483-y
34 Kim MN, Han K, Yoo J, Hwang SG, Ahn SH. Increased risk of hepatocellular carcinoma and mortality in chronic viral hepatitis with concurrent fatty liver. *Aliment Pharmacol Ther* 2022;55:97-107. doi:10.1111/apt.16706
35 Chung GE, Cho EJ, Yoo JJ, et al. Young adults with nonalcoholic fatty liver disease, defined using the fatty liver index, can be at increased risk of myocardial infarction or stroke. *Diabetes Obes Metab* 2022;24:465-72. doi:10.1111/dom.14597
36 Sattar N, Rawshani A, Franzén S, et al. Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks. *Circulation* 2019;139:2228-37. doi:10.1161/CIRCULATIONAHA.118.037885
37 Santos RD, Valenti L, Romeo S. Does nonalcoholic fatty liver disease cause cardiovascular disease? Current knowledge and gaps. *Atherosclerosis* 2019;282:110-20. doi:10.1016/j.atherosclerosis.2019.01.029
38 Brouwers MCGJ, Simons N, Stehouwer CDA, Isaacs A. Non-alcoholic fatty liver disease and cardiovascular disease: assessing the evidence for causality. *Diabetologia* 2020;63:253-60. doi:10.1007/s00125-019-05024-3
39 Biondi-Zoccai GG, Abbate A, Liuzzo G, Biasucci LM. Atherothrombosis, inflammation, and diabetes. *J Am Coll Cardiol* 2003;41:1071-7. doi:10.1016/S0735-1097(03)00088-3
40 Cusi K. Treatment of patients with type 2 diabetes and non-alcoholic fatty liver disease: current approaches and future directions. *Diabetologia* 2016;59:1112-20. doi:10.1007/s00125-016-3952-1
41 Kim JH, Kwon SY, Lee SW, Lee CH. Validation of fatty liver index and lipid accumulation product for predicting fatty liver in Korean population. *Liver Int* 2011;31:1600-1. doi:10.1111/j.1478-3231.2011.02580.x

Web appendix: Supplementary figures
Web appendix: Supplementary tables