



# Cardiovascular Disease, Cancer, and Mortality Among People With Type 2 Diabetes and Alcoholic or Nonalcoholic Fatty Liver Disease Hospital Admission

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## OBJECTIVE

To describe associations between alcoholic liver disease (ALD) or nonalcoholic fatty liver disease (NAFLD) hospital admission and cardiovascular disease (CVD), cancer, and mortality in people with type 2 diabetes mellitus (T2DM).

## RESEARCH DESIGN AND METHODS

We performed a retrospective cohort study by using linked population-based routine data from diabetes registry, hospital, cancer, and death records for people aged 40–89 years diagnosed with T2DM in Scotland between 2004 and 2013 who had one or more hospital admission records. Liver disease and outcomes were identified by using ICD-9 and ICD-10 codes. We estimated hazard ratios (HRs) from Cox proportional hazards regression models, adjusting for key risk factors.

## RESULTS

A total of 134,368 people with T2DM (1,707 with ALD and 1,452 with NAFLD) were studied, with a mean follow-up of 4.3 years for CVD and 4.7 years for mortality. Among those with ALD, NAFLD, or without liver disease hospital records 378, 320, and 21,873 CVD events; 268, 176, and 15,101 cancers; and 724, 221, and 16,203 deaths were reported, respectively. For ALD and NAFLD, respectively, adjusted HRs (95% CIs) compared with the group with no record of liver disease were 1.59 (1.43, 1.76) and 1.70 (1.52, 1.90) for CVD, 40.3 (28.8, 56.5) and 19.12 (11.71, 31.2) for hepatocellular carcinoma (HCC), 1.28 (1.12, 1.47) and 1.10 (0.94, 1.29) for non-HCC cancer, and 4.86 (4.50, 5.24) and 1.60 (1.40, 1.83) for all-cause mortality.

## CONCLUSIONS

Hospital records of ALD or NAFLD are associated to varying degrees with an increased risk of CVD, cancer, and mortality among people with T2DM.

Alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes mellitus (T2DM) are common diseases, and ALD or NAFLD often coexist with T2DM. Evidence of a bidirectional relationship exists between liver disease and T2DM. Both ALD and NAFLD appear to be risk factors for T2DM, and T2DM is a risk factor for more-severe liver disease in people with ALD or NAFLD (1–6). The increased risk of cardiovascular disease (CVD), cancer, and mortality among people with T2DM compared with those without diabetes is well known (7–9). Evidence of an association

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\*A complete list of the members of the Scottish Diabetes Research Network Epidemiology Group can be found in the Supplementary Data online.

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exists between NAFLD and CVD among people with and without diabetes, although more information is needed in terms of describing the natural history of NAFLD with regard to both its hepatic and its extrahepatic complications (10,11). On the basis of existing evidence, more advanced liver disease seems to be associated with a higher risk of complications (11,12). Fewer data are available for the association between ALD and key health outcomes in people with T2DM. How alcoholic or nonalcoholic etiology influences the risk of complications of liver disease is not clear (13), although a fatty liver probably confers an increased cardiovascular risk regardless of etiology and lipid phenotype (14).

In a Danish cohort of patients with cirrhosis, of whom 10% had diabetes (and 25% had any comorbidity), comorbidity was associated with synergistic increases in mortality compared with a matched control population (15). Another Danish study compared the incidence of several comorbidities (including diabetes) identified from hospital records over a median of 2.6 years in people with a hospital diagnosis of alcoholic cirrhosis or no record of viral hepatitis or the outcomes of interest with age- and sex-matched control subjects without cirrhosis (16). During follow-up, 738 subjects developed diabetes (hazard ratio [HR] 5.54 [95% CI 4.94, 6.21]). The authors noted that the extremely high mortality among subjects with ALD meant that few lived long enough to develop a comorbidity and a potential existed for confounding by cigarette smoking. We have not identified any studies of the effect of ALD on mortality, CVD, and cancer among people with T2DM.

Limited evidence exists for the association between NAFLD and mortality or CVD in people with T2DM. A U.S. cohort study of 337 people with T2DM, of whom 116 were diagnosed with NAFLD on the basis of imaging or liver biopsy specimen, suggested that NAFLD is associated with increased all-cause mortality (age, sex, and duration of diabetes adjusted HR 2.2 [95% CI 1.1, 4.2], mean follow-up 10.5 years) (17). An Italian study of 2,103 people with T2DM, of whom 157 had NAFLD, showed that NAFLD is associated with an increased risk of incident CVD over 6.5 years (HR 1.9 [95% CI 1.2, 2.6] adjusted for age, sex, smoking, diabetes duration, LDL cholesterol, medication, and the metabolic syndrome) (18).

Currently, identifying diagnoses of common liver diseases from routinely collected health data at a whole-population level is not possible. However, ALD and NAFLD can be identified from hospital records in large population-based studies with record linkage to identify morbidity and mortality. This study describes event rates for CVD, cancer, and mortality among a T2DM cohort of people with ALD or NAFLD and those without records of liver disease. The study also compares relative risks of CVD, cancer, and all-cause and cause-specific mortality for ALD and NAFLD compared with no record of liver disease within the T2DM cohort.

## RESEARCH DESIGN AND METHODS

### Study Population and Survival Time

We conducted a retrospective cohort study of data from a 2014 extract of the Scottish Care Information – Diabetes Collaboration (SCI-DC) national population-based register (19) for people diagnosed with T2DM in Scotland between 1 January 2004 and 31 December 2013, who were 40–89 years of age during the study period, and who had a record of one or more hospital admissions. The Information Services Division of National Health Service (NHS) National Services Scotland linked the diabetes data to national mortality, cancer registry, and hospital discharge records. Generation of the anonymized linked data set was approved by the Scotland A Multicentre Research Ethics Committee (reference 11-AL-0225), Caldicott guardians, and the NHS National Services Scotland Privacy Application Committee (reference 33/11).

We excluded people with ICD-9 and ICD-10 codes for viral hepatitis, autoimmune hepatitis, hemochromatosis, and any cirrhosis, fibrosis, sclerosis, or portal hypertension with no mention of ALD or NAFLD. Table 1 shows the ICD-9 and ICD-10 codes used to identify these conditions. Entry date to the cohort was the date of T2DM diagnosis. Exit date for CVD and cancer analyses was based on the date of the first CVD event or cancer registration after diagnosis of diabetes or 31 December 2013 for people who neither died nor had a CVD or cancer event recorded by that date, with censoring at the date of death where appropriate. Exit date for mortality analyses was date of death or 31 December 2013 for survivors to that date. Follow-up was censored at the date of death as a result of another cause for cause-specific

mortality. Survival time for each analysis was from date of diagnosis of diabetes to censoring or the date of exit.

### Exposure and Outcomes

ALD and NAFLD were identified from the presence of the ICD-9 and ICD-10 codes listed in the relevant columns of Table 1 in any diagnosis field of a hospital admission record either before or after a T2DM diagnosis or in a death record. Individuals with records of both ALD and NAFLD ( $n = 116$ ) were classified as having ALD because mention of ALD suggests that alcohol intake would have been higher than that allowed for a diagnosis of NAFLD at some point in the patient's history.

CVD and date of event was identified from the presence of CVD codes as listed in Table 1 in any position on death and hospital records. Cancer events were identified from cancer registry and death records. Date of death was derived from national mortality records. Cause-specific mortality was defined by using the codes listed in Table 1 in the primary cause of death field, derived from national mortality records.

### Statistical Analysis

To perform a complete case analysis, we excluded people with missing data and compared the characteristics of people with and without complete data. Cox proportional hazards regression models were fitted in which ALD or NAFLD were the exposures. Models were adjusted for age, sex, socioeconomic status (SES) (described below), smoking status (current, former, and never), hypertension/antihypertensive treatment (defined below), high cholesterol/lipid-lowering treatment (defined below), glycated hemoglobin (HbA<sub>1c</sub>) by using measures closest to the date of T2DM diagnosis, and record of CVD history before T2DM diagnosis.

We used the Scottish Index of Multiple Deprivation (SIMD) as the measure of SES (20). SIMD is a small-area–based ranked measure that combines 38 indicators of deprivation across seven domains. Rankings of the 6,505 geographical areas recorded in SIMD were included in models as quintiles of the distribution, where the first and fifth quintiles correspond to the most- and least-deprived groups in the population, respectively.

The binary marker of hypertension/antihypertensive treatment was derived from measured blood pressure ( $\geq 140$  mmHg systolic or  $\geq 90$  mmHg

**Table 1—ICD-9 and ICD-10 codes used to define disease groups of interest**

Disease group	Individual disease name	Diagnosis/procedure code*
Viral hepatitis	Viral hepatitis	D070.3, D070.5, D070.9, B16, B17, B18
Autoimmune hepatitis and primary biliary cirrhosis	Autoimmune hepatitis and primary biliary cirrhosis	571.4, 571.6, K75.4, K74.3
Hemochromatosis	Hemochromatosis	275.0, E83.1
Unspecified liver disease	Cirrhosis	571.5, K74.6
	Hepatic fibrosis or sclerosis or fibrosis with sclerosis	571.9, K74.0, K74.1, K74.2
	Portal hypertension	572.3, K76.6
ALD	ALD	571.0, 571.2, 571.3, K70
NAFLD	Other chronic nonalcoholic liver disease	571.8, K76
	NASH	K75.8
CVD mortality	Coronary heart disease	I20–I25
	Cerebrovascular disease	I60–I69, G45
	Heart failure	I50
	Sudden cardiac death	I46.1
Liver disease mortality	All liver disease except HCC, toxic liver disease, and liver diseases classified elsewhere	K70, K72–76
Other mortality	All other causes of death	Any code not in the above four cells
Prevalent and incident CVD	Acute coronary syndrome	410, I20–I22
	Myocardial infarction	431–437, I61, I63, I64
	Stroke	428, I50
	Heart failure	K40–K46, K49, K50.1
	Coronary revascularization procedure and carotid revascularization procedure	K50.8, K75, L29.4, L29.5, L31.1, L34.4
HCC	HCC	C22.0
Other cancer mortality	All cancer except HCC	All C codes except C22.0

\*ICD-9 codes are numerical, ICD-10 codes are alphanumerical, and fourth revision of the Office for Population Censuses and Surveys procedure codes are given in italics. All deaths were coded on the basis of ICD-10.

diastolic) or prescription history of antihypertensive medications (ACE inhibitors, angiotensin II antagonists,  $\beta$ -blocking agents, calcium channel blockers, or diuretics) by using data recorded closest to the diagnosis of T2DM. A similar approach was used to construct the high cholesterol/lipid-lowering treatment indicator, which combined measured values of serum cholesterol  $>5$  mmol/L and prescription records for lipid-modifying medications.

Little evidence of interaction between liver disease status and sex was observed; the two exceptions were marginally significant at the conventional 5% level: 1) For hepatocellular carcinoma (HCC) mortality, the interaction of ALD with sex yielded  $P = 0.04$ , and 2) for non-HCC mortality, the interaction of NAFLD and non-alcoholic steatohepatitis (NASH) with sex yielded  $P = 0.05$ . All other interaction terms yielded  $P > 0.1$ . We therefore adjusted for sex instead of constructed sex-specific models.

In sensitivity analyses, we excluded individuals with prevalent CVD or cancer at T2DM diagnosis from an additional Cox

model as described above and omitted the prevalent CVD or cancer variables to describe the association between ALD or NAFLD and incident CVD or incident cancer after T2DM diagnosis. All Cox models were fitted by using the PHREG procedure in SAS 9.4 statistical software. Differences in direct adjusted survival curves between people with and without ALD or NAFLD were obtained by using SAS routines published by Wang and Zhang (21) and are presented graphically.

## RESULTS

We identified a cohort of 134,368 people age 40–89 years diagnosed with T2DM during the study period and who had a record of at least one hospital admission and no record of viral hepatitis, autoimmune hepatitis, hemochromatosis, or liver disease of unspecified cause and complete data for SES, smoking status, hypertension/antihypertensive treatment, high cholesterol/lipid-lowering treatment, and HbA<sub>1c</sub> (Supplementary Fig. 1). Distribution of characteristics of

people excluded because of missing data was similar to those without liver disease in the study cohort. Mean age at T2DM diagnosis was 62.7 years in both groups. The proportion of men was 54.0% in those with missing data versus 54.9% in those with no liver disease, and the corresponding respective proportions with prevalent CVD were 19.2% and 19.1%.

The study cohort therefore included 134,368 people. Mean follow-up varied between 4.3 years for CVD outcomes and 4.7 years for mortality. There were 1,707 people (1.3%) with a record of ALD and 1,452 (1.1%) with a record of NAFLD, of whom 8.9% and 19%, respectively, had a record of liver biopsy. For the ALD group, the mean age at the first ALD-related hospital admission was 57.4 years, and mean age at T2DM diagnosis was 59.3 years. For the NAFLD group, the mean age at the first NAFLD-related hospital admission was 58.3 years, and mean age at T2DM diagnosis was 58.7 years. Statistically significant differences were found for many characteristics by liver disease status, partly reflecting

the large sample size even when absolute differences were small and of questionable clinical relevance (Table 2). Key differences between groups were that people with a history of hospital admission with ALD and NAFLD were younger than the group without liver disease, a larger proportion of men and smokers was found in the ALD group, and a smaller proportion of men was found in the NAFLD group than in the other groups. Mean BMI was lowest in the ALD group and highest in the NAFLD group. The number of outcomes, duration of follow-up, and crude event rates by liver disease status are shown in Table 3. The most

common causes of death among the other causes groups, regardless of liver disease status, were respiratory disease, which accounted for ~18% of other deaths in the ALD group and 30% of other deaths in the NAFLD and no liver disease groups. Diseases of the digestive system (including liver disease) accounted for 18% of other deaths in the ALD, 14% in the NAFLD, and 10% in the no liver disease groups. Other cardiovascular and endocrine diseases contributed 12% and 10%, 18% and 14%, and 17% and 11%, respectively, to the other causes of death groups for people with ALD, NAFLD, and no liver disease.

Table 4 shows adjusted HR estimates derived from Cox models for the associations between ALD or NAFLD and the outcomes of interest. Lung cancer was the most common specific cancer among the ALD and no liver disease groups, but colorectal cancer was the most common cancer among people with a history of NAFLD. None of the associations between liver disease and individual common cancers was statistically significant.

The association with incident/recurrent CVD was similar for both types of liver disease. HRs for all-cause mortality were elevated for both liver disease groups and were higher for the ALD group than for the NAFLD group. The association with non-HCC-related incidence was statistically significant for the ALD group.

The sensitivity analyses excluding people with prevalent CVD or cancer at T2DM diagnosis resulted in similar associations to those for recurrent/incident CVD and cancer (Supplementary Table 1). The differences in direct adjusted survival between people with and without a history of hospital admission with ALD or NAFLD derived from all-cause mortality are shown in Supplementary Figs. 2 and 3, respectively. Declines in survival relative to the no liver disease group over time were much steeper for the ALD group than for the NAFLD group.

## CONCLUSIONS

Novel data in a national cohort show that people with T2DM who have a hospital record of either ALD or NAFLD are at increased risk of mortality as a result of all causes, CVD, and HCC as well as are at increased risk for incident/recurrent CVD events compared with those without a record of liver disease. These findings extend those from previous studies of outcomes of cirrhosis in general populations (23–25) by including a wider definition of liver disease and nonfatal outcomes, separating the NAFLD group from the broader non-alcoholic cirrhosis group, describing CVD incidence in both ALD and NAFLD groups, and limiting the study population to people with T2DM.

The largest study to date of a general population (the Third National Health and Nutrition Examination Survey [NHANES III]) that is relevant to the current NAFLD data investigated the association between hepatic steatosis and NASH identified from a retrospective examination of

**Table 2—Descriptive characteristics of people aged 40–89 years diagnosed with T2DM in Scotland between 2004 and 2013 with record of one or more hospital admission and complete data by liver disease status**

Variable	ALD (n = 1,707)	NAFLD (n = 1,452)	No liver disease (n = 131,209)
Age at T2DM diagnosis (years)	59.3 ± 9.8	58.7 ± 11.0	62.7 ± 12.0
P value	< 0.001*	< 0.001*	
Male sex	1,219 (71.4)	685 (47.2)	72,017 (54.9)
P value	< 0.001†	< 0.001†	
Deprivation (SIMD quintile)			
1 (most deprived)	593 (34.7)	348 (24.0)	30,745 (23.4)
2	405 (23.7)	367 (25.3)	30,111 (22.9)
3	276 (16.2)	275 (18.9)	26,769 (20.4)
4	250 (14.6)	260 (17.9)	24,270 (18.5)
5 (least deprived)	183 (10.7)	202 (13.9)	19,314 (14.7)
P value	< 0.001‡	0.201‡	
HbA <sub>1c</sub> (mmol/mol)§	60.6 ± 25.6	63.7 ± 21.9	63.1 ± 22.6
P value	< 0.001	0.008	
BMI (kg/m <sup>2</sup> )§¶	29.5 ± 6.5	33.6 ± 6.6	32.1 ± 6.4
P value	< 0.001*	0.082#	
Smoking status			
Current	770 (45.1)	375 (25.8)	29,409 (22.4)
Former	489 (28.6)	500 (34.4)	47,916 (36.5)
Never	448 (26.2)	577 (39.7)	53,884 (41.1)
P value	< 0.001‡	0.008‡	
Systolic blood pressure (mmHg)§**	135 ± 19.5	137 ± 17.7	138 ± 17.9
P value	< 0.001*	0.002#	
Hypertension/antihypertensive treatment	1,568 (91.9)	1,307 (90.0)	115,623 (88.1)
P value	< 0.001†	0.027†	
Total cholesterol (mmol/L)§***	5.0 ± 1.5	5.2 ± 1.5	5.1 ± 1.3
P value	< 0.001*	0.021*	
High cholesterol/lipid-lowering treatment	1,314 (77.0)	1,309 (90.2)	120,209 (91.5)
P value	< 0.001†	0.073†	
History of CVD before T2DM	315 (18.4)	276 (19.0)	25,008 (19.1)
P value	0.556†	1.000†	
History of cancer before T2DM	188 (11.0)	259 (17.8)	20,687 (15.8)
P value	< 0.001†	0.033†	

Data are mean ± SD or n (%). All hypothesis test results (P values) represent the comparison of ALD or NAFLD group with the no liver disease group. \*Two-sample t test (equality of variances rejected, so degrees of freedom derived through Satterthwaite approximation [22]). †Fisher exact test. ‡χ<sup>2</sup> test. §Value is that measured at the closest point in time to the date of T2DM diagnosis. ||Mann-Whitney test. ¶Numbers of missing values are as follows: 449 (ALD), 359 (NAFLD/NASH), and 32,828 (no liver disease). #Two-sample t test (equality of variances assumption upheld). \*\*Numbers of missing values are as follows: 10 (ALD), 11 (NAFLD/NASH), and 528 (no liver disease). \*\*\*Numbers of missing values are as follows: 15 (ALD), 15 (NAFLD), and 1,542 (no liver disease).

**Table 3—Outcomes, duration of follow-up, and crude event rates for people aged 40–89 years diagnosed with T2DM in Scotland between 2004 and 2013 with one or more hospital admission records and complete data by liver disease status**

Outcome	ALD (n = 1,707)			NAFLD (n = 1,452)			No liver disease (n = 131,209)		
	Events	PY	Event rates per 1,000 PY	Events	PY	Event rates per 1,000 PY	Events	PY	Event rates per 1,000 PY
Incident/recurrent CVD	378	6,746	56.0	320	6,219	51.5	21,873	567,204	38.6
Incident/recurrent HCC	64	7,262	8.8	19	7,054	2.7	114	618,794	0.2
Incident/recurrent cancer, excluding HCC	204	7,003	29.1	157	6,720	23.4	14,987	586,336	25.6
Mortality		7,346			7,092			618,872	
All-cause	724		98.6	221		31.2	16,203		26.2
CVD	75		10.2	41		5.8	4,428		7.2
HCC	36		4.9	8		1.1	153		0.2
Cancer, excluding HCC	72		9.8	38		5.4	5,474		8.8
Other	179		24.4	80		11.3	6,133		9.9

PY, person-years.

ultrasound images originally performed to identify gallstones and liver enzyme concentrations measured in 1988–1994 and mortality up to 2006 (26). Mortality as a result of all causes, CVD, cancer, or liver disease among people with steatosis or steatohepatitis was similar to that among those without steatosis. NHANES III participants likely had mild liver disease, as emphasized in the correspondence after publication of the article (27). Resolution of mild liver disease among some NHANES III participants during follow-up as a result of lifestyle changes is plausible (28). Resolution of mild NAFLD over time would be expected to attenuate any association between liver disease at baseline and premature mortality. In contrast to the population-based sample and retrospective review of ultrasound

images in NHANES III, another important difference is that the current study was undertaken in an older population of people with T2DM, among whom NAFLD was identified from hospital records.

A recent study reported heterogeneous associations between alcohol consumption and CVD and found stronger associations between heavy alcohol intake and fatal CVD (compared with nonfatal disease) consistent with the current findings for the association between ALD and CVD mortality and incident/recurrent CVD (29). The current study findings showing an association between NAFLD and CVD are consistent with a recent systematic review and meta-analysis of data from 16 prospective and retrospective studies that were not limited to people with diabetes (11). The meta-analysis included 34,043

people among whom 36% had NAFLD identified by imaging or biopsy specimen, and ~2,600 CVD outcomes occurred over a median of ~7 years of follow-up. The random-effects summary odds ratio for the association between NAFLD and CVD was 1.64 (95% CI 1.26, 2.13) (11). Our point estimates for the association between NAFLD and both all-cause mortality and CVD outcomes are similar to those of the small cohort studies described earlier (17,18), but our estimates are more precise as would be expected given the larger study population.

A large Finnish study identified an increased incidence of multiple types of cancer in addition to HCC among people with severe ALD (30), and the current study possibly lacked the power to detect these associations. NAFLD has been associated with an increased risk of colon cancer (31), adenomatous polyps (32), and right-sided colonic tumors (33). Additional research is required to establish whether NAFLD is associated with other extrahepatic cancers.

As for all studies that use routine data, misclassification was possible in the current study. We identified NAFLD from hospital records in 1.1% of people with T2DM and at least one hospital admission record, a considerably smaller proportion than reported in population-based studies of people with T2DM that have been able to characterize liver disease status more accurately (34,35). The proportion we found is closer to the prevalence of clinically significant liver disease identified by liver ultrasound and noninvasive measures of NASH, hepatic fibrosis, and systemic inflammation of 2.2% in participants in

**Table 4—Associations between history of hospital admission with ALD or NAFLD and incident/recurrent CVD, cancer, and mortality among people aged 40–89 years diagnosed with T2DM in Scotland between 2004 and 2013 with record of one or more hospital admission and no record of other chronic liver disease**

Outcome	HR (95% CI)	
	ALD (n = 1,707)	NAFLD (n = 1,452)
Incident/recurrent CVD event*	1.59 (1.43, 1.76)	1.70 (1.52, 1.90)
Incident/recurrent HCC†	41.7 (30.0, 57.8)	19.3 (11.8, 31.4)
Incident/recurrent cancer, excluding HCC‡	1.28 (1.12, 1.47)	1.10 (0.94, 1.29)
All-cause mortality§	4.85 (4.49, 5.23)	1.60 (1.40, 1.83)
CVD mortality*	2.05 (1.63, 2.58)	1.15 (0.85, 1.57)
HCC mortality†	20.5 (13.9, 30.1)	6.16 (3.02, 12.6)
Cancer mortality, excluding HCC‡	1.24 (0.98, 1.57)	0.76 (0.55, 1.04)
Other causes of death	3.50 (3.00, 4.07)	1.60 (1.28, 1.99)

HRs are expressed relative to group with no record of any of the specified liver disease types (n = 131,209). See RESEARCH DESIGN AND METHODS for definitions. \*Model includes prevalent CVD (i.e., CVD diagnosed before T2DM) as additional predictor. †Model includes prevalent HCC as additional predictor. ‡Model includes prevalent non-HCC as additional predictor. §Model includes prevalent CVD and prevalent cancer (any site) as additional predictors.

the Edinburgh Type 2 Diabetes Study (34). Markers of liver injury have only recently been included in the diabetes electronic health record and were not available for use as an alternative marker of liver disease in the current study.

We were unable to identify people with diagnoses of liver disease established solely in ambulatory care, and such individuals likely have less-severe liver disease than people with a diagnosis in hospital admission records. The absolute event rates we report for the various liver disease groups, therefore, are likely to be applicable to people with T2DM and more-advanced liver disease. Except for the associations between ALD and all-cause mortality and between both types of liver disease and HCC incidence and mortality, the strength of the associations between liver disease and other outcomes was modest (HRs <1.70). However, people with liver disease diagnosed solely in ambulatory care and those with undiagnosed liver disease, who form a large subgroup of people with T2DM, were included in the comparison group. The absolute risks of the outcomes of interest in this subgroup of people who, in general, have less-severe liver disease are expected to be intermediate between those without liver disease and those with severe liver disease who were likely to have formed the majority of our study population with a hospital admission record of liver disease (11,12). Consequently, we expect that the relative risks describing the association between severe liver disease and outcomes of interest would be larger than we reported if we had been able to exclude people with liver disease from the comparison group. An estimate of the size of this presumed bias is only possible when there are robust ways of identifying people with all levels of severity of liver disease and their risk of outcomes of interest at a population level. Our estimates of the strength of the association between NAFLD and mortality or CVD are consistent with those of other studies that included people with the whole spectrum of NAFLD and in which fewer concerns existed about ascertainment and misclassification bias (11,17,18). Thus, the opposing effect of the different biases in the way we identified the NAFLD and comparison groups are approximately balanced, but this hypothesis requires testing when suitable data are available. The exclusion of people with missing data on covariates may

have influenced the strength of the associations we observed, but as noted above, the characteristics of people with missing data were similar to those of people without liver disease.

Although we identified differing HRs for outcomes by liver disease status for all-cause mortality and cancer, the association between liver disease and an increased risk of incident/recurrent CVD is similar for both ALD and NAFLD. Despite the noted concerns about potential bias in the current study, the association between NAFLD and incident/recurrent CVD is similar to that reported in a meta-analysis of studies that included people without diabetes and used other ways of identifying NAFLD (11). These findings suggest that liver disease per se influences risk of CVD, although that common risk factors underlie the risk of both liver disease and CVD remains possible.

We could not identify the date of diagnosis of liver disease and assumed that liver disease was present at T2DM diagnosis. Mean age at T2DM diagnosis and at hospital admission with first mention of liver disease was similar, suggesting that liver disease is likely to have been present before a T2DM diagnosis in many people. The study included a relatively short median follow-up time because we only used data from 2004, the point from which the diabetes register in Scotland was almost complete. Any time-varying effect of liver disease can only be investigated in a large, well-characterized cohort of people that includes repeated assessment of liver disease and diabetes status.

The strengths of our study include the population-based nature of the national electronic record that captures data for >99% of people with a T2DM diagnosis in Scotland and the availability of linkage to quality-assured hospital admission, cancer registry, and mortality data for the whole population (36). We excluded people with no record of hospital admission from the comparator group to reduce bias that could arise from inclusion of a healthier subgroup of people with T2DM and people who had not had the opportunity to have liver disease or outcomes of interest ascertained by investigations performed during a hospital admission. We believe that despite the limitations discussed above, the approach we took is the most appropriate for identifying liver disease through routine health care data in population-based studies. A

description of longer-term outcomes of the history of hospital admission with liver disease will be possible in future data linkages.

The data from a national cohort of people with T2DM show for the first time in our knowledge that a history of hospital admission with ALD or NAFLD is associated with increases in incident/recurrent CVD, cancer, and all-cause and selected cause-specific mortality and independently of major risk factors. This measure of ALD or NAFLD, therefore, is associated with further increases in risk of early mortality, CVD, and cancer among people with T2DM beyond the risks associated with T2DM and key risk factors alone (7–9). The early stages of ALD and NAFLD are reversible after lifestyle changes, such as a reduction in alcohol consumption, weight loss, and increases in physical activity. The data suggest that clinicians should support their patients with T2DM and liver disease to make lifestyle changes where appropriate to reduce the risk of mortality and morbidity associated with more-severe liver disease as well as to improve glycemic control. Although some evidence of benefit of pioglitazone in patients with NAFLD exists (37), adverse effects of this agent have precluded its widespread use. Treatment with glucagon-like peptide 1 receptor agonists is effective for hyperglycemia in many patients with T2DM, and treatment with liraglutide has shown promise in some patients with NASH (38). However, because no licensed treatments for chronic liver disease exist and lifestyle change is notoriously difficult to achieve, additional research is needed to identify effective treatments for both liver disease and its extrahepatic complications among people with T2DM and to establish the role of differential follow-up among people with T2DM and liver disease.

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