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

*Sarah H. Wild,[1] Jeremy J. Walker,[1] Joanne R. Morling,[2] David A. McAllister,[1] Helen M. Colhoun,[3] Bassam Farran,[3] Stuart McGurnaghan,[3] Rory McCrimmon,[4] Stephanie H. Read,[1] Naveed Sattar,[5] and Christopher D. Byrne,[6,7] on behalf of the Scottish Diabetes Research Network Epidemiology Group**

Diabetes Care 2018;41:341–347 | https://doi.org/10.2337/dc17-1590

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

[1]*Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, U.K.*
[2]*Division of Epidemiology and Public Health, University of Nottingham, Nottingham, U.K.*
[3]*Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, U.K.*
[4]*Division of Molecular and Clinical Medicine, University of Dundee, Dundee, U.K.*
[5]*Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, U.K.*
[6]*Nutrition and Metabolism, Faculty of Medicine, University of Southampton, Southampton, U.K.*
[7]*National Institute for Health Research Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, U.K.*

Corresponding author: Sarah H. Wild, sarah.wild@ed.ac.uk.

Received 1 August 2017 and accepted 20 October 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-1590/-/DC1.

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

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_{1c}) 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 (≥140 mmHg systolic or ≥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, β-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 nonalcoholic 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_{1c} (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 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_{1c} (mmol/mol)§	60.6 ± 25.6	63.7 ± 21.9	63.1 ± 22.6
P value	< 0.001‖	0.008‖	
BMI (kg/m^2)§¶	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^2 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 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 nonalcoholic 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 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

	ALD (n = 1,707)			NAFLD (n = 1,452)			No liver disease (n = 131,209)		
Outcome	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

	HR (95% CI)	
Outcome	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.

Acknowledgments. The authors thank the health care staff, people with diabetes, the SCI-DC Steering Group, the Scottish Diabetes Group, the Scottish Diabetes Survey Group, clinical network managers, and staff of each NHS Board for providing data and setting up, maintaining, and overseeing the SCI-DC.

Funding. This work was supported by funding from the Scottish Government through the Scottish Diabetes Group. The Scottish Diabetes Research Network is supported by NHS Research Scotland, a partnership of Scottish NHS Boards and the Chief Scientist Office of the Scottish Government. N.S. received European Federation

of Pharmaceutical Industries and Associations Innovative Medicines Initiative Joint Undertaking grant number 115372, which partially supports his contribution to this article. C.D.B. is supported in part by the Southampton National Institute for Health Research Biomedical Research Centre. Data linkage was funded by the Scottish Government through the Scottish Diabetes Group.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. S.H.W., J.J.W., J.R.M., D.A.M., H.M.C., B.F., S.M., R.M., S.H.R., N.S., and C.D.B. contributed to the data interpretation, critically reviewed the manuscript for important intellectual content, and approved the final version. S.H.W., J.J.W., and C.D.B. wrote the first draft of the manuscript. S.H.W., J.J.W., J.R.M., and C.D.B. designed the study and the analysis plan; data were acquired as part of routine clinical care. S.H.W. and C.D.B performed the literature search. J.J.W. prepared and analyzed the data and prepared the figures. H.M.C., B.F., and S.M. contributed to the generation of data. S.H.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the Diabetes UK Professional Conference, Manchester, U.K., 8–10 March 2017, and the 53rd Annual Meeting of the European Association for the Study of Diabetes, Lisbon, Portugal, 11–15 September 2017.

References

1. Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. J Hepatol 2000;32:209–217
2. Holstein A, Hinze S, Thiessen E, Plaschke A, Egberts EH. Clinical implications of hepatogenous diabetes in liver cirrhosis. J Gastroenterol Hepatol 2002;17:677–681
3. Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. Am J Med 2007; 120:829–834
4. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol 2015;62:1148–1155
5. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol 2015;62(Suppl.):S47–S64
6. Raff EJ, Kakati D, Bloomer JR, Shoreibah M, Rasheed K, Singal AK. Diabetes mellitus predicts occurrence of cirrhosis and hepatocellular cancer in alcoholic liver and non-alcoholic fatty liver diseases. J Clin Transl Hepatol 2015;3:9–16
7. Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med 2015;373:1720–1732
8. Walker JJ, Brewster DH, Colhoun HM, et al.; Scottish Diabetes Research Network (SDRN) Epidemiology Group. Type 2 diabetes, socioeconomic status and risk of cancer in Scotland 2001-2007. Diabetologia 2013;56:1712–1715
9. Sarwar N, Gao P, Seshasai SR, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies [published correction appears in Lancet 2010;376:958]. Lancet 2010;375: 2215–2222
10. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 2010;363:1341–1350
11. 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
12. Lonardo A, Sookoian S, Pirola CJ, Targher G. Non-alcoholic fatty liver disease and risk of cardiovascular disease. Metabolism 2016;65:1136–1150
13. Völzke H. Multicausality in fatty liver disease: is there a rationale to distinguish between alcoholic and non-alcoholic origin? World J Gastroenterol 2012;18:3492–3501
14. Loria P, Marchesini G, Nascimbeni F, et al. Cardiovascular risk, lipidemic phenotype and steatosis. A comparative analysis of cirrhotic and non-cirrhotic liver disease due to varying etiology. Atherosclerosis 2014;232:99–109
15. Jepsen P, Vilstrup H, Andersen PK, Lash TL, Sørensen HT. Comorbidity and survival of Danish cirrhosis patients: a nationwide population-based cohort study. Hepatology 2008;48:214–220
16. Jepsen P, Lash TL, Vilstrup H. The clinical course of alcoholic cirrhosis: development of comorbid diseases. A Danish nationwide cohort study. Liver Int 2016;36:1696–1703
17. Adams LA, Harmsen S, St Sauver JL, et al. Nonalcoholic fatty liver disease increases risk of death among patients with diabetes: a community-based cohort study. Am J Gastroenterol 2010; 105:1567–1573
18. Targher G, Bertolini L, Padovani R, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 2007;30: 1212–1218
19. McKnight JA, Morris AD, Cline D, Peden N, Fischbacher C, Wild S; Scottish Diabetes Survey Monitoring Group. Implementing a national quality assurance system for diabetes care: the Scottish Diabetes Survey 2001-2006. Diabet Med 2008;25:743–746
20. Scottish Government National Statistics. Scottish Index of Multiple Deprivation: 2009 general report. Available from http://www.gov.scot/Resource/Doc/933/0115249.pdf. Accessed 22 September 2016
21. Wang H, Zhang X. Confidence band for the difference between two direct adjusted survival curves. J Stat Software 2016;70:code snippet 2
22. Satterthwaite FE. An approximate distribution of estimates of variance components. Biometrics Bull 1946;2:110–114
23. Sørensen HT, Thulstrup AM, Mellemkjar L, et al. Long-term survival and cause-specific mortality in patients with cirrhosis of the liver: a nationwide cohort study in Denmark. J Clin Epidemiol 2003;56:88–93
24. Roberts SE, Goldacre MJ, Yeates D. Trends in mortality after hospital admission for liver cirrhosis in an English population from 1968 to 1999. Gut 2005;54:1615–1621
25. Ratib S, Fleming KM, Crooks CJ, Walker AJ, West J. Causes of death in people with liver cirrhosis in England compared with the general population: a population-based cohort study. Am J Gastroenterol 2015;110:1149–1158
26. Lazo M, Hernaez R, Bonekamp S, et al. Nonalcoholic fatty liver disease and mortality among US adults: prospective cohort study. BMJ 2011; 343:d6891
27. Jepsen P, Grønbæk H. Prognosis and staging of non-alcoholic fatty liver disease. BMJ 2011;343: d7302
28. Sung KC, Ryu S, Lee JY, Kim JY, Wild SH, Byrne CD. Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver. J Hepatol 2016;65:791–797
29. Bell S, Daskalopoulou M, Rapsomaniki E, et al. Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. BMJ 2017;356: j909
30. Sahlman P, Nissinen M, Pukkala E, Färkkilä M. Cancer incidence among alcoholic liver disease patients in Finland: a retrospective registry study during years 1996-2013. Int J Cancer 2016;138: 2616–2621
31. Sanna C, Rosso C, Marietti M, Bugianesi E. Non-alcoholic fatty liver disease and extra-hepatic cancers. Int J Mol Sci 2016;17:17
32. Hwang ST, Cho YK, Park JH, et al. Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps. J Gastroenterol Hepatol 2010;25:562–567
33. Wong VW, Wong GL, Tsang SW, et al. High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. Gut 2011;60: 829–836
34. Morling JR, Fallowfield JA, Guha IN, et al. Clinically significant chronic liver disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. QJM 2016;109:249–256
35. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274–285
36. ISD Scotland. Data quality assurance: products and services. Available at http://www.isdscotland.org/Products-and-Services/Data-Quality/Assessments. Accessed 22 September 2016
37. Rotman Y, Sanyal AJ. Current and upcoming pharmacotherapy for non-alcoholic fatty liver disease. Gut 2017;66:180–190
38. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679–690