Research Article

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Type 2 diabetes and risk of hospital admission or death for chronic liver diseases

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Background & Aims: The impact of type 2 diabetes (T2DM) on hospital admissions and deaths due to common chronic liver diseases (CLDs) is uncertain. Our aim was to investigate associations between T2DM and CLDs in a national retrospective cohort study and to investigate the role of sex and socio-economic status (SES).

Methods: We used International Classification of Disease codes to identify incident alcoholic liver disease (ALD), autoimmune liver disease, haemochromatosis, hepatocellular carcinoma, non-alcoholic fatty liver disease (NAFLD) and viral liver disease from linked diabetes, hospital, cancer and death records for people of 40–89 years of age in Scotland 2004–2013. We used quasi Poisson regression to estimate rate ratios (RR).

Results: There were 6667 and 33624 first mentions of CLD in hospital, cancer and death records over ~1.8 and 24 million person-years in people with and without T2DM, respectively. The most common liver disease was ALD among people without diabetes and was NAFLD among people with T2DM. Age-adjusted RR for T2DM compared to the non-diabetic population (95% confidence intervals) varied between 1.27 (1.04–1.55) for autoimmune liver disease and 5.36 (4.41–6.51) for NAFLD. RRs were lower for men than women and for more compared to less deprived populations for both ALD and NAFLD.

Conclusions: T2DM is associated with increased risk of hospital admission or death for all common CLDs and the strength of the association varies by type of CLD, sex and SES. Increasing prevalence of T2DM is likely to result in increasing burden of all CLDs.

Keywords: Diabetes; Liver disease; Cohort.

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Abbreviations: T2DM, type 2 diabetes; CLD, chronic liver disease; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; SES, socio-economic status; RR, rate ratio; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; SIMD, Scottish index of multiple deprivation; T1DM, type 1 diabetes; BMI, body mass index; SCI-DC, Scottish care information, diabetes collaboration.

Introduction

Mortality from liver disease in the United Kingdom (UK) has increased by 400% since the 1970s, in contrast to reductions in mortality from cardiovascular disease and some cancers [1]. Similar increases in CLD mortality have also been observed in the United States (US) [2] although cirrhosis mortality has declined by 50–60% in France and Italy between 1980 and 2010 [3]. Incidence and prevalence of common chronic liver diseases (CLDs) including alcoholic liver disease (ALD) and obesity-related non-alcoholic fatty liver disease (NAFLD) and their complications have increased in the UK and US [4,5]. Age-standardised incidence and mortality from hepatocellular carcinoma (HCC), a complication of many CLDs, have increased approximately two-fold in the UK in the last 40 years [4] and in other European countries (see http://globocan.iarc.fr/old/FactSheets/cancers/liver-new.asp). It is well known that type 2 diabetes (T2DM) is associated with increased risk of the whole spectrum of NAFLD and its complications including non-alcoholic steatohepatitis (NASH), cirrhosis and HCC [6–9], but the effect of T2DM on other common types of CLD is less clear.

Estimating the burden of ill health attributable to CLDs is difficult due to the lack of accurate, non-invasive diagnostic tests

that can be applied within population-based studies. The available tests have been predominantly validated in high prevalence (secondary care) populations and may be less accurate in the wider population. Routine healthcare data obtained from hospital admission, cancer registration and death records provides a source of readily available data that have been used previously to assess the burden of serious gastro-intestinal disease in the US [5]. Although hospital admission and cancer registration data are likely to underestimate prevalence of disease they provide valuable information for health care planning and an estimate of the burden of serious liver disease.

Increasing global prevalence of T2DM and the inverse influence of socio-economic status (SES) on T2DM prevalence in high income countries are well established [10,11]. The inverse relationship between SES and ALD has also been described in several populations [12,13] and the incidence of HCC in England between 1990 and 2009 was higher among people living in materially deprived areas than among people living in less deprived areas [14]. However, it is not known whether SES influences the association between T2DM and CLDs, as it does for T2DM and cardiovascular disease [15]. The need for further research on the contribution of SES to disparities in incidence, treatment and outcomes of liver disease has previously been identified [16,17].

The aim of this retrospective cohort study in a national population of approximately five million people was: a) to describe numbers and rates of first record of CLD hospital admission or death for people with and without T2DM and, b) to investigate associations between T2DM and CLD hospital admissions and deaths, establishing whether associations differed by sex or SES.

Materials and methods

Datasets

We used data from the population-based Scottish diabetes register linked to national hospital, cancer and death records in a retrospective cohort study design. The Scottish diabetes register is derived from primary and secondary care records for people with diabetes diagnosed in normal clinical practice using blood glucose measurements and/or HbA1c with coverage of >99% since 2004 [18] the start of the study period. Validation of the diabetes register for clinical practice occurs through responses to annual invitations to diabetic retinopathy screening. For example, in 2010 191,571 individuals were invited for screening of whom 2% were suspended from the screening programme due to the person not having diabetes (see http://www.sci-diabetes.scot.nhs.uk/project-overview/). In addition, validation of the research extract, performed against hospital admissions mentioning diabetes [18] or against sulphonylurea prescriptions (unpublished data) suggests that over 99% of people with diagnosed diabetes in Scotland are included in both clinical and research databases.

Definition of CLD

CLD was identified from the first mention in any position (primary/underlying or secondary diagnosis or cause of death) in national hospital in-patient, cancer and mortality records and grouped into categories using codes from the ninth (ICD-9) and tenth [ICD-10] International Classification of Diseases revisions as follows:

- ALD: (571.0), (571.2), (571.3), [K70].
- autoimmune hepatitis and primary biliary cirrhosis: (571.4), (571.6), [K75.4, K74.3].
- hemochromatosis: (275.0) [E83.1].
- hepatocellular carcinoma (HCC): (155.0); [C22.0].
- NAFLD: a category incorporating the following ICD-defined categories: other chronic non-alcoholic liver disease: (571.8), non-alcoholic fatty liver disease: [K76.0], non-alcoholic steatohepatitis: [K75.8], cirrhosis (571.5) [K74.6], hepatic fibrosis or sclerosis or fibrosis with sclerosis (571.9) [K74.0, K74.1, K74.2] or portal hypertension: (572.3) [K76.6] that was not attributed to any of the other liver disease categories.
- viral hepatitis: (D070.3), (D070.5), (D070.9); [B16, B17, B18];

The study size was determined by the number of incident CLDs occurring in the national population in the study time period which ended in December 2013, based on the most recent data available to the research team.

An area-based measure of SES is assigned to residents of Scotland on the basis of where they live using the Scottish Index of Multiple Deprivation (SIMD) (for more information see http://www.scotland.gov.uk/Topics/Statistics/SIMD). SIMD 2009 combines 31 indicators across seven domains: income/employment, health, education, housing, geographic access, and crime. The index is generated from a weighted sum of the seven domain scores for each area defined by postcodes which contains a median of 769 people. Quintiles of the index were used to define approximately equal fifths of the distribution at a national level, and Q1 and Q5 were used to identify the most and least deprived quintiles (or fifths) respectively.

Study design and data analysis

We used a dynamic population-based retrospective study design using aggregated data for the total population of Scotland and individual level data on people with diabetes. Inclusion criteria for estimation of the person-years denominator were being aged 40 to 89 years in Scotland between 2004 and 2013. The only exclusion criteria were the approximately 1% of hospital admissions or death records with missing SIMD data and the events and person-years for people with type 1 diabetes. For each CLD group, with the exception of NAFLD, the first recorded event was identified independently (so, for example, a record of hemochromatosis followed by a subsequent record of viral hepatitis contributes to event counts and person-years denominator for both disease groups). Event counts and person-years at risk for NAFLD were identified by excluding records with any mention of ALD, viral disease, hemochromatosis or autoimmune liver disease. Records that mentioned HCC and NAFLD and no other specific CLD were counted in both HCC and NAFLD groups.

Routine national healthcare data were used to identify CLD events occurring between January 1 2004 and December 31 2013 for adults aged 40–89 years. For each CLD, people with prevalent disease prior to January 2004 defined by the presence of a relevant disease code in hospital or cancer records in the previous 10 years were excluded. Follow-up time was censored for each CLD at first event or death from any cause. We included deaths from CLDs and HCC where they represented the record of CLD or HCC and there was no previous hospital or cancer record of CLD or HCC. Numbers of CLD events, person-years at risk and rates were estimated by diabetes status, age, sex, and SIMD quintile.

Mid-year population estimates for Scotland by age, sex, calendar year, and SIMD quintile for the relevant years were obtained from National Records of Scotland. Data for the non-diabetic population were identified by subtracting numbers of incident events and person-years at risk for the population of people with type 1 diabetes (T1DM) and T2DM from numbers of CLD events and person-years at risk calculated from mid-year populations for the whole of Scotland. Type of diabetes was based on clinical records and a validation algorithm that used information on age at diagnosis of diabetes with additional validation using dates and type of diabetes treatment, dates of first HbA1c >6.5% (48 mmol/mol) and invitation to diabetic retinopathy screening [19].

Absolute incidence rates were used to describe patterns of different CLDs in the study population, with direct standardisation for age, stratification by sex and, where appropriate, for SIMD quintile, using the 2007 mid-year population of Scotland as the standard. Rate ratios (RR) for people with T2DM compared to people without diabetes were estimated using quasi Poisson regression modelling to control for potential confounding by age and to allow for the over-dispersed nature of the distribution of the data. Likelihood ratio tests were used to test for interactions between T2DM and sex and T2DM and SES. Analyses were stratified by sex and also for SES where appropriate. Exploratory analyses were performed among people with type 1 diabetes.

Sensitivity analyses were performed to identify whether the associations with T2DM altered if the following alternative outcome definitions were used:

1. Primary diagnoses/underlying cause of death of ALD and NAFLD (excluding mention of ALD or NAFLD in secondary positions in hospital and death records)
2. Hospital admission records mentioning ALD and NAFLD in any position (excluding deaths with no prior record of hospital admission)