Research Article

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Overweight in late adolescence predicts development of severe liver disease later in life: A 39 years follow-up study

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Background & Aims: The increased prevalence of overweight has been suggested to contribute to the worldwide increase in liver diseases. We investigated if body mass index (BMI) in late adolescence predicts development of severe liver disease later in life.
Methods: We performed a cohort study using data from 44,248 men (18–20 years) conscribed to military service in Sweden between 1969 and 1970. Outcome data were collected from national registers to identify any diagnosis of severe liver disease (i.e., diagnosis of decompensated liver disease, cirrhosis or death in liver disease) until the end of 2009. A Cox regression model was applied using BMI as independent variable. The model was adjusted for use of alcohol, use of narcotics, smoking, high blood pressure and cognitive ability at time of conscription.
Results: During a follow-up period of a mean of 37.8 years, 393 men were diagnosed with severe liver disease (mean time to diagnosis 24.7 years). BMI (Hazard ratio [HR] = 1.05 for each unit increase in BMI, 95% confidence interval [CI]: 1.01–1.09, $p = 0.008$) and overweight (HR = 1.64 for BMI 25–30 compared to BMI 18.5–22.5, 95% CI: 1.16–2.32, $p = 0.006$) were associated with an increased risk of development of severe liver disease.
Conclusions: Being overweight in late adolescence is a significant predictor of severe liver disease later in life in men.
Lay summary: We investigated close to 45,000 Swedish men in their late teens enlisted for conscription in 1969–1970. After almost 40 years of follow-up, we found that being overweight was a risk factor for developing severe liver disease, independent of established risk factors such as alcohol consumption.

Keywords: Body mass index; Long-term follow-up; Epidemiology; Decompensated liver disease; Cirrhosis.
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Abbreviations: BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; ICD, international classification of disease; HR, hazard ratio; CI, confidence interval; NPR, National Patient Register; CDR, Causes of Death Register.

Introduction

Liver disease is a common cause of morbidity and mortality worldwide [1]. Chronic liver diseases can in some individuals lead to cirrhosis, which is associated with an increased risk of mortality. The prognosis is particularly unfavourable if decompensated liver disease occurs [2].

It is clinically difficult to identify individuals in the general population with an increased risk for development of cirrhosis and severe liver disease later in life. Knowledge of predictive factors is necessary in order to outline effective prevention programs for liver disease. Several liver diseases, especially non-alcoholic fatty liver disease (NAFLD), have shown an increasing prevalence globally over the last few decades [3–5]. During this period, the prevalence of overweight, defined as a body mass index (BMI) above 25, and obesity, defined as a BMI above 30, have increased in both Europe and the USA, as well as globally [6]. Obesity in adults has been linked to an increased risk for liver-related death or hospitalization both in persons with [7,8] and without [9–11] known liver disease, as well as a higher risk for hepatocellular carcinoma (HCC) [12,13]. In addition, overweight and obesity are associated with a worse prognosis in several liver diseases, such as NAFLD [14], hepatitis B and C [15,16] and alcoholic liver disease [17,18].

Alcohol consumption and use of narcotics are other known risk factors for liver disease. However, previous studies on the prediction of liver disease have included adults where it has not been possible to eliminate reversed causality; alcohol consumption may cause obesity, while being overweight may be a marker of alcohol consumption rather than a risk factor of its own. Whether or not overweight in late adolescence is associated with development of severe liver disease later in life, independent of the use of alcohol or narcotics, has not been studied.

We examined if high BMI in late adolescence in a population of well-characterized adolescent men was associated with an increased risk of a severe liver disease, defined as a diagnosis of decompensated liver disease, cirrhosis or liver-related mortality later in life.

Materials and methods

Study population

We used data from a nationwide, population-based study conducted during 1969–1970 of all Swedish men enlisted for conscription. During that time, conscription was mandatory in Sweden, and only 2–3% of men were exempted from conscription, mostly due to severe disabilities or diseases. This study was based on 49,321 Swedish men, age 18–20, included at that time.

Variables

Baseline

All conscripts underwent an extensive health examination and personal interviews, and filled out questionnaires on alcohol consumption, smoking, use of narcotics and self-rated health.

Body mass index. We used data on height and weight to calculate BMI (kg/m^2). Conscripts were considered underweight if they had a BMI <18.5. A BMI of 18.5-<22.5 was classified as low normal, and used as a reference category, a BMI of 22.5-<25 was defined as high normal, while overweight was classified as a BMI of 25-<30 and obesity as BMI $\geqslant$30.

Alcohol consumption. Weekly alcohol consumption was classified as either absent, 1–100 g per week, 101–250 g per week or above 250 g of pure alcohol per week.

Smoking. Smoking at the time of conscription was classified as either absent, between 1–5 cigarettes per day, 6–10 cigarettes per day, 11–20 cigarettes per day, or more than 20 cigarettes per day.

Use of narcotics. Use of narcotics was defined as present if the conscript had tried or was actively using any drug, except for alcohol and tobacco, at the time of conscription.

High blood pressure. Blood pressure was classified as high if a systolic blood pressure of >140 mmHg or a diastolic blood pressure of >90 mmHg was noted at the time of conscription.

Self-rated health. Self-rated health is a morbidity and mortality predictor even after adjustment of key covariates such as co-morbidity and is commonly used in epidemiological studies as a measure of overall health status [19]. Self-rated health was assessed using the question "In general, would you say your health right now is: very good (1), good (2), fair (3), poor (4) or very poor (5)?"

Cognitive ability and cardiovascular fitness. A test of cognitive ability was performed as described elsewhere [20,21]. The test has been found to be a predictor of mortality in the cohort independent of BMI, alcohol use and smoking [20]. Cardiovascular fitness using an ergometer cycle has been found to be a predictor of myocardial infarction independent of BMI [22]. This was tested at baseline when the mens' maximum work capacity divided by body weight, was assessed and transformed into a numeric scale [23]. For both tests, the men received a score from 1 to 9, a higher number indicates a better result.

Follow-up

All Swedish citizens are assigned a personal identity number a few days after immigration or birth [24], this data was available at the time of conscription.

The National Patient Register (NPR) was established in 1964, and includes information on dates of hospital admissions, discharges, and diagnoses classified according to International Classification of Diseases (ICD) codes, 7–10. The register also includes information on hospital-based outpatient visits since 2001. The coverage of the register is approximately 99% of all somatic discharge diagnoses, and the validity of hospital discharge diagnoses is between 85–95% depending on diagnosis [25].

The Causes of Death Register (CDR) contains data from 1961 regarding the causes of death of all Swedish citizens, including if the person died abroad. It is mandatory for the responsible physician to report the underlying cause of death (e.g., stroke) and any disease that could have contributed to the death of the individual (e.g., atrial fibrillation).

Primary endpoint: severe liver disease

We used diagnoses of liver cirrhosis, decompensated liver disease (HCC, ascites, esophageal varices (bleeding or not bleeding), hepatorenal syndrome or hepatic encephalopathy) or specific coding for liver failure from the NPR, or death from any of the above in the CDR as our primary endpoint variable, severe liver disease. ICD codes for the diagnoses used in the present study are listed in the supplementary material (Supplementary Table 1).

Statistical analysis

We excluded 431 persons due to missing (N = 422) or likely incorrectly recorded height (above 2.3 or under 0.8 meters, N = 5) or weight (above 200 or under 30 kg, N = 4). We excluded a further 4642 men due to missing data regarding any of the covariates, leaving a final sample of 44,248 men. A flowchart for participant inclusion in the analyses is presented in Fig. 1. All analyses were performed in STATA 13.0 (StataCorp, College Station, Texas, USA) and a two-sided alpha value of 0.05 was used to test for statistical significance.

Descriptives

Descriptive data are presented per BMI category. Dichotomous and categorical variables are presented as percentage and continuous variables are presented as mean values. The association with BMI as a continuous variable is calculated using Mann-Whitney rank sum test for dichotomous variables, and Spearman rank correlation for categorical and continuous variables.

Survival analysis

A multivariate Cox regression model was used to assess the effect of BMI on the outcome of any manifestation of severe liver disease. We tested BMI both as a continuous and as a categorical variable. We used a stepwise forward approach to identify any potential parameter associated with the primary outcome variable of severe liver disease, using a p value of $\leqslant$0.1 as significant. We constructed one crude univariate model per parameter and one multivariate model including all significant parameters. The final models with BMI as a continuous variable and BMI as a categorical variable were consequently adjusted for alcohol consumption, use of narcotics, smoking, cognitive ability and high blood pressure at conscription (n = 44,248). Estimates of the final models are presented as hazard ratios (HR). The models were tested for proportionality using Schoenfeld residuals, with no evidence of violation.

The men were followed until the first registered diagnosis of severe liver disease, death of any cause, emigration or the end of the follow-up period. After emigration the men were considered lost to follow-up but contributed with the time until emigration to the analysis.

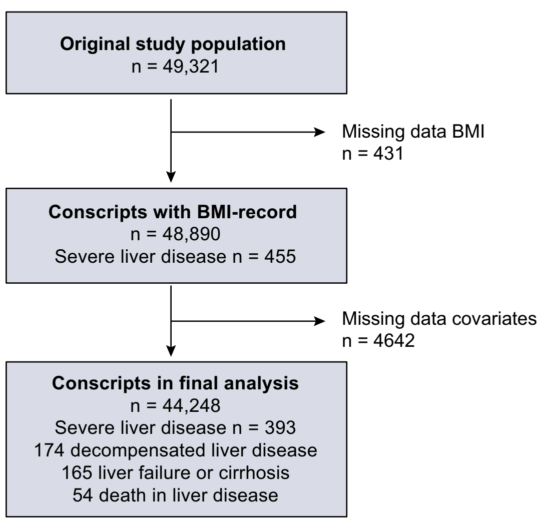

Fig. 1. Flowchart for participant inclusion.