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Original Research Article

Substitutions of saturated fat intakes with other macronutrients and foods and risk of NAFLD cirrhosis and all-cause hepatocellular carcinoma: a prospective cohort study

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A B S T R A C T

Background: Short-term trials have shown a reduction in liver fat when saturated fatty acids (SFAs) are substituted with polyunsaturated fatty acids (PUFA), or with low-glycemic carbohydrates. However, few cohort studies have been conducted to investigate the associations of replacing SFA and SFA-rich foods with different macronutrients and foods in more severe stages of liver disease; nonalcoholic fatty liver disease (NAFLD) cirrhosis and hepatocellular carcinoma (HCC).

Objectives: To investigate associations between the substitution of SFA and SFA-rich foods with other macronutrients and foods and NAFLD cirrhosis and HCC in a middle-aged to elderly Swedish population of $n = 77{,}059$ males and females.

Methods: Time-to-event analyses were performed to investigate associations between the food and macronutrient substitutions and NAFLD cirrhosis and HCC. Multivariable Cox regression models were constructed to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Statistical isocaloric and equal-mass substitutions were performed using the leave-one-out method. Prespecified nutrient and food substitutions of interest were SFA with carbohydrates, SFA with fiber, SFA with PUFA, butter with margarine and vegetable oils, unprocessed red meat with fish, and milk with fermented milk.

Results: Over a median follow-up of 24 y, 566 cases of NAFLD cirrhosis and 205 cases of HCC were registered. Overall, dietary substitutions showed no clear associations with either NAFLD cirrhosis or HCC. Substituting SFA with carbohydrates showed an HR of 0.87 (95% CI: 0.74, 1.02) for HCC and 1.00 (95% CI: 0.89, 1.11) for NAFLD cirrhosis. Substituting milk with fermented milk showed an HR of 0.93 (95% CI: 0.85, 1.01) for HCC and 0.97 (95% CI: 0.92, 1.03) for NAFLD cirrhosis.

Conclusions: No clear associations were observed between diet and NAFLD cirrhosis or HCC. Although accompanied by low precision, possible lowered risks of HCC by substituting SFA with carbohydrates or milk with fermented milk might be of interest, but needs replication in other cohorts.

Keywords: saturated fat, NAFLD, cirrhosis, HCC, substitutions

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver diseases, with an estimated global prevalence of 32%–38% [1]. NAFLD is defined by the presence of fat droplets in >5% of hepatocytes that is not caused by alcohol [2]. Nonalcoholic steatohepatitis (NASH), the more inflammatory state of NAFLD, may in turn progress to fibrosis, cirrhosis, and eventually hepatocellular carcinoma (HCC) [2]. Cirrhosis because of NAFLD is projected to increase globally over the next 5–10 y, resulting in increased healthcare resources and costs [3]. As NAFLD cirrhosis is strongly associated with incident HCC, extrahepatic cancers, and all-cause mortality [4,5], more research effort should be put into preventive strategies.

Abbreviations: ALD, alcoholic liver disease; CI, confidence interval; COSM, Cohort of Swedish Men; CVD, cardiovascular disease; DAG, directed acyclic graph; FFQ, food frequency questionnaire; HCC, hepatocellular carcinoma; HR, hazard ratio; ICD, International Classification of Diseases; MASLD, metabolic-dysfunction-associated steatotic liver disease; MICE, multivariate imputation by chained equations; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NPR, National Patient Register; PPV, positive predictive value; RCT, randomized controlled trial; SMC, Swedish Mammography Cohort; T2D, type-2 diabetes; TFA, trans fatty acid.

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To disentangle the role of isolated nutrients and foods in NAFLD, both randomized controlled trials (RCT) and observational studies are needed. We have repeatedly shown that replacing SFA with PUFA decreases liver fat over 7–10 wk, both during eucaloric and hypercaloric conditions [6–8]. Less data are available on other macronutrients, for example, carbohydrates, and foods than PUFA, although some data suggest replacing SFA with carbohydrates may also reduce liver fat [9]. Thus, with regard to NAFLD, SFA appears to be a key dietary factor to replace in the diet. However, short-term intervention studies are not suitable to investigate the role of diet on more severe forms of NAFLD that may take decades to develop, for example, cirrhosis. Observational studies of long-term exposure-outcome associations have shown that people who report consuming more red and processed red meat have an increased risk of developing NAFLD and cirrhosis compared with those consuming less [10]. Few studies have however specified the food or foods for which red and processed red meat have been substituted with, making it difficult to translate those findings into practical food recommendations. The same applies to other foods such as yogurt, whereby total energy intake has been adjusted for but without specifying any clear food substitutions [11,12]. Although adjusting for total energy intake is often justified in observational studies of dietary exposures, the implications of such adjustment (that is, vague causal estimands, confounding bias, and external validity issues) are not always appreciated [13,14]. Specifying the replacement food or nutrient using statistical substitution analyses may thus help to mitigate some of these issues [15]. To our knowledge, no study has investigated diet in relation to NAFLD-associated cirrhosis on a population-based level.

Moreover, NAFLD cirrhosis may progress to HCC, a cancer subtype constituting 90% of total primary liver cancers [16]. However, although NAFLD-associated HCC is rapidly increasing, HCC is also caused by other risk factors such as viral hepatitis and alcohol consumption [17]. Because of the low incident rates of HCC in the general population, it is somewhat difficult to investigate cause-specific HCC in observational cohort studies. Nevertheless, increased research efforts for the prevention of all-cause HCC are highly warranted as the long-term survival prognosis of this cancer is relatively poor.

Our main research aim was therefore to investigate the associations between substituting SFA and SFA-rich food sources with other macronutrients and food sources on NAFLD cirrhosis and all-cause HCC in a middle-aged to elderly population of males and females in Sweden.

Methods

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Review Board at Karolinska Institute in Stockholm, Sweden. Study consent was provided if the participant completed and returned the questionnaires. The Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM) both belong to the National Research Infrastructure Swedish infrastructure for medical population-based life-course and environmental research (SIMPLER) (www.simpler4health.se).

Study population

SMC and COSM were initiated in 1987 and 1997, respectively, with the aim to investigate associations between dietary exposures and chronic disease outcomes [18]. Individuals in each cohort are followed up with questionnaires on diet and lifestyle every decade (that is, for SMC: 1987, 1997, 2008/2009, and 2019 and for COSM: 1997, 2008/2009, and 2019). Baseline information from 1997 was used for the primary analysis in this study and the SMC and COSM cohorts were pooled.

A complete flowchart of the cohort study is shown in Figure 1. A total of $n = 56{,}030$ females in the SMC cohort and $n = 100{,}303$ males in the COSM cohort were asked to participate. Out of a pooled sample of $n = 156{,}333$ individuals, $n = 88{,}077$ agreed to participate (56%). After excluding individuals with an incorrect or missing personal identification number, other missing data, cancer diagnosis before baseline (including HCC), death before baseline, as well as potential energy misreporters (<800 or >4200 kcal for males and <500 and >3500 kcal for females), $n = 79{,}729$ individuals remained and constituted the study sample for HCC as the outcome. For the primary outcome (NAFLD cirrhosis), individuals with alcohol consumption >20 g/d for females and >30 g/d for males were excluded. In addition, individuals with a diagnosis of any liver disease before baseline, as defined under outcome ascertainment, were excluded, leaving a final study sample size of $n = 77{,}059$.

Exposure assessment

Baseline diet (1997) was assessed using a validated self-administered food frequency questionnaire (FFQ), covering 96 different food and beverage items. The same FFQ was used in both cohorts. Response categories ranged from never to $\geq$3 times/d. The FFQ also contained open-ended questions on foods and beverages commonly consumed in Sweden, such as bread, dairy, sugar, honey, coffee, tea, soft drinks, and beer. Average intakes of foods and beverages for each participant were estimated by multiplying the frequency of each item by age-specific portion sizes. Absolute values of each item were subsequently linked to the Swedish Food Agency food composition database for the estimation of nutrient intakes. The version of the food composition database aligned with the time by which the baseline diet was assessed. Total energy intake was calculated as the sum of energy from SFA, MUFA, PUFA, carbohydrates, fiber, protein, and alcohol. Conversion factors for carbohydrates and protein were 17 kJ/g, for fat 37 kJ/g, for alcohol 29 kJ/g, and for fiber 8 kJ/g. The total amount of kJ was then divided by 4.184 to attain energy in the unit of kcal. Total food intake was calculated as the sum of grams from all foods and beverages.

Foods were categorized into 10 food categories: unprocessed red meat, fish, milk (0.5%–3% fat content), fermented milk (0.5% to $\geq$3% fat content), butter, margarine and vegetable oils, sweets, alcoholic beverages, fruits and vegetables, and other foods. Missing information on foods and food groups was treated as zero consumption. A detailed categorization of the foods can be found in Supplemental Table 1.

The FFQ used by SMC and COSM in 1997 has been validated against multiple 24-h recall interviews, dietary records, and fatty acid biomarkers from subcutaneous adipose tissue [19–23]. Correlation coefficients between the FFQ and 7-d dietary food records were: 0.76 for carbohydrates, 0.7 for fermented milk, and 0.3–0.7 for red and processed red meat. Correlation coefficients between the FFQ and fourteen 24-h recall interviews were 0.75 for SFA and 0.49 for PUFA [19]. The follow-up questionnaire used in 2009 was extended to contain 132 food items, capturing new foods on the market [24]. Similar categorization of food items was conducted in 2009 as for the food groups defined in 1997.

Isocaloric substitutions

The leave-one-out method was used to model isocaloric substitutions in this population. This method has been shown to perform equally well as the energy partition method for estimating the relative

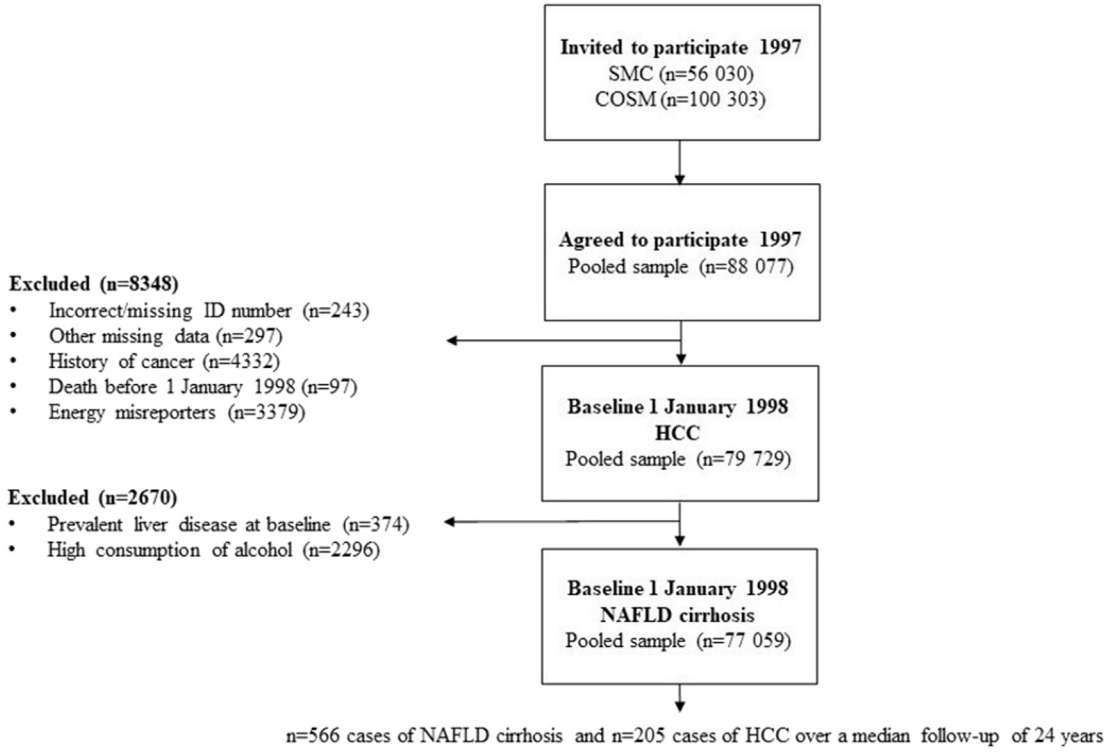

FIGURE 1. Participant flowchart in the pooled study sample of the COSM and SMC cohorts. COSM, Cohort of Swedish Men; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; SMC, Swedish Mammography Cohort.

substitution effects of a single food or nutrient [15]. Nutrients were expressed in energy (kcal). A composite variable of total energy intake was calculated from the sum of all nutrients. To estimate the effect of substituting x amount of kcal of SFA with x amount of kcal of PUFA, the following model was defined as follows:

$$\text{Log}(h(t; x)) \text{ of replacing SFA with PUFA} = \log(h_0(t)) + \beta_{1\text{PUFA(kcal)}} + \beta_{2\text{MUFA(kcal)}} + \beta_{3\text{Carbohydrates(kcal)}} + \beta_{4\text{Fiber(kcal)}} + \beta_{5\text{Protein(kcal)}} + \beta_{6\text{Alcohol(kcal)}} + \beta_{7\text{Totalenergyintake(kcal)}} + \beta_{8\ldots\text{Confounders}}$$

Food items were expressed in g/d instead of kcal/d. Equal-mass substitutions were modeled using the leave-one-out method [15]. In order for the substitutions to approach meaningful isocaloric replacements, foods that were similar in their energy content were compared against each other. A composite variable of total grams per day was calculated from the sum of all foods in grams. To estimate the effect of substituting x amount of grams of unprocessed red meat with x amount of grams of fish, the following model was defined as follows:

$$\text{Log}(h(t; x)) \text{ of replacing red meat with fish} = \log(h_0(t)) + \beta_{1\text{Fish(g)}} + \beta_{2\text{Butter(g)}} + \beta_{3\text{Margarineandvegetableoil(g)}} + \beta_{4\text{Milk(g)}} + \beta_{5\text{Fermentedmilk(g)}} + \beta_{6\text{Alcoholicbeverages(g)}} + \beta_{7\text{Sweets(g)}} + \beta_{8\text{F\&V(g)}} + \beta_{9\text{Otherfoods(g)}} + \beta_{10\text{Totalfoodmass(g)}} + \beta_{11\ldots\text{Confounders}}$$

Total energy intake and total food intake were included as composite variables to *1*) emulate a setting by which comparator groups in a hypothetical RCT are matched by energy or total grams of food and *2*) to account for unobserved confounding by common determinants of dietary intake that are correlated with total energy intake/total food intake (for example, metabolic efficiency and body size) [13]. Six nutrient and food substitutions were prespecified, namely, SFA with PUFA, SFA with carbohydrates, SFA with fiber, unprocessed red meat with fish, butter with margarine and vegetable oil, and milk with fermented milk. No other food substitutions were deemed feasible because of the potential of introducing nonisocaloric comparator groups when modeling equal-mass substitutions [for example, nuts (600 kcal/100 g) compared with fermented milk (50 kcal/100 g)]. SFA was not compared with either MUFA or protein as these 3 nutrients coexist in many foods (particularly in a non-Mediterranean population), making it difficult to interpret the meaning of such replacements. All models aimed to compare a substitution of 50 kcal of nutrients/foods, corresponding to around 2.5 E% in a diet of 2000 kcal, except for SFA compared with fiber that used 20 kcal as the unit. For food substitutions, 50 kcal corresponded to 5 g for butter compared with vegetable oil, 30 g for unprocessed red meat compared with fish and 100 g for milk compared with fermented milk. Units of exposure were chosen based on the practical relevance of the substitution and the distribution of foods and macronutrients in the population.

Selection of confounding variables

Potential confounders were selected based on the background literature and directed acyclic graphs (DAGs), using the online DAGitty software tool (Dagitty.net) (Supplemental Figure 1) [25,26]. To estimate relative substitution effects of replacing SFA with other macronutrients or SFA-rich foods with other foods, the following adjustment set was identified: age [y (continuous, linear form)], sex [males/females (categorical)], total energy intake or total food intake [kcal or g (continuous, linear form)], dietary variables specified in each leave-one-out model [kcal or g (continuous, linear form)], current smoking status [never/former/current smoker (categorical)], education [primary school ≤9 y, high school 10–12 y, or university >12 y (categorical)], family history of cardiovascular disease (CVD) [yes/no if either mother or father have had a myocardial infarction before the age of 60 (categorical)], physical activity [<1, 1, 2–3, 4–5, or >5 h/wk of exercise (categorical)], sleep [h/d (continuous, linear form)], previous diet [kcal or g (continuous, linear form)], and BMI [<18.5 kg/m^2, 18.5–24.9 kg/m^2, 25–30 kg/m^2, and >30 kg/m^2 (categorical)].

To separate temporality between diet and BMI and mitigate risk of conditioning on a potential mediator, BMI was estimated from the weight reported by the participant ≥5 y before baseline (that is, for a participant with the age of 66 in 1997, self-reported weight from the age of 60 was used, whereas, for a participant with the age of 76 in 1997, self-reported weight from the age of 70 was used), assuming no change in height over this time period. Total energy intake and total food intake were included as proxy variables for common determinants of dietary intake (described under "Isocaloric substitutions"). Family history of CVD was included as a proxy variable for underlying genetic susceptibility of metabolic diseases. Previous diet (defined as all macronutrients or food groups specified for the different substitution models) was included as an unobserved confounder in the DAG. All confounding variables identified were self-reported from questionnaires received in 1997.

Outcome ascertainment

After the initiation of this project, the nomenclature of NAFLD was redefined to metabolic-dysfunction-associated steatotic liver disease (MASLD) with some minor modifications to the disease criteria [27]. As NAFLD is highly overlapping (>99.5%) with MASLD, we decided to keep the initial definition of NAFLD [28].

Information on liver diseases was retrieved from the Swedish National Patient Register (NPR) and the Cause of Death Register, whereas information on HCC was retrieved from the Swedish Cancer Register and the Cause of Death Register. NAFLD cirrhosis was defined as having a diagnosis of unspecified cirrhosis or complications of cirrhosis (such as portal hypertension or gastric and esophageal varices) with no other concomitant liver disease associated with cirrhosis, except for NAFLD and NASH (please see Supplemental Table 2 for a detailed description of the outcomes). The above definition was guided by a recent expert panel consensus statement of using administrative coding in electronic health records to define NAFLD [29]. HCC was defined as having a diagnosis corresponding to the International Classification of Diseases for Oncology (ICD-O) code C22.0 (ICD-O/2) or ICD-10 code C22.0. Prevalent cases of HCC at baseline were excluded for both the primary and secondary outcomes. For NAFLD cirrhosis, individuals with prevalent liver diseases at baseline defined in Supplemental Table 2 were excluded. Positive predictive values (PPVs) for several liver diseases used to define NAFLD cirrhosis and HCC in the Swedish registries are high, ranging from 84% for HCC to 96% for esophageal varices [30]. The PPV for unspecific cirrhosis to the liver (K74.6) is 91%, whereas the PPV for NAFLD (K76.0) is 82%–91%, although higher (95%–96%) in those with type-2 diabetes and obesity [30,31].

Statistical analysis

Multivariable Cox proportional hazard regression models were used to estimate hazard ratios (HR) with corresponding 95% confidence intervals (CI), with time since baseline as the underlying timescale. The 2 main models were adjusted for age, sex, education, sleep, smoking, family history of CVD, BMI, physical activity, total energy intake (for macronutrients), total food intake (for foods), and other dietary variables necessary for estimating the joint substitution effect. For both the primary (NAFLD cirrhosis) and secondary (HCC) outcomes, participants were followed up from January 1, 1998, until the date of outcome diagnosis, death, or administrative end of follow-up (December 31, 2021), whichever occurred first. For NAFLD cirrhosis, participants were censored when diagnosed with other liver diseases associated with cirrhosis, specified in Supplemental Table 2. Multivariate imputation by chained equations (MICE) ($n = 5$ imputations) was used to account for missing data on baseline covariates (ranging from 0.4% for education to 13% for BMI for both outcomes), assuming the data was missing at random or missing completely at random. MICE was performed using the *mice* package in R. Pooling of parameter estimates was done using Rubin's rules. The assumption of proportional hazards was examined and confirmed using Schoenfeld residual plots.

To examine the robustness of the results, a couple of sensitivity analyses were performed:

1) Complete-case analyses were conducted to examine selection bias because of missing data on confounders.
2) The first 2 y of follow-up were excluded to examine the potential for reverse causation.
3) The category named "other foods" was further subcategorized into cereals, processed red meat, and all other remaining foods. This was done to examine residual confounding bias from grouping foods with potentially different effects on the outcome into 1 composite food group. Both cereals and processed red meat constituted a large proportion of foods in the original food group, hence the decision to separate them.
4) To examine the potential for misclassification bias of the primary outcome and accommodate the new nomenclature of MASLD [20], we only counted NAFLD cirrhosis cases for those who had a history of diagnosis of T2D, hyperlipidemia, hypertension, or had a BMI ≥25 kg/m^2 at baseline.
5) The Swedish Cancer Register has been shown to underreport incident HCC cases [32]. To examine the potential of underreporting, the Swedish Cancer Register and the Cause of Death Register were combined with the NPR (for those who had any concomitant liver disease at the time of HCC diagnosis) to define HCC.
6) As diet is a time-varying exposure, previous diet may confound the association between baseline diet and the outcome. To examine the potential for confounding bias from previous dietary intake (before the questionnaire received in 1997), we updated the baseline from 1998 to 2009 and further adjusted for dietary variables assessed in 1997 in a second analysis, in combination with covariates from 2009 (BMI was assessed from the questionnaire in 1997) (Supplemental Figure 1). Extrahepatic cancers before baseline were not excluded in this analysis. Because of few incident HCC cases after 2009, we performed these analyses only on the primary outcome with the assumption that any unmeasured confounding from previous dietary intake would bias the estimate between diet and HCC in the same direction (although with different strengths) as for NAFLD cirrhosis. We furthermore assumed a similar direction and strength of confounding for prebaseline diet on estimates derived from baseline 1998 as for the direction and strength of confounding for diet in 1997 on estimates derived from baseline 2009.

All analyses were conducted using R (R Core Team) version 3.6.0.

Results

Over a median follow-up of 24 y, 566 cases of NAFLD cirrhosis and 205 cases of HCC were registered. Population characteristics are presented in Table 1. The average age of the study population was 60.0 (53.0–69.0) y, 17% had a university degree and 24% were current smokers. The average intake of SFA was 14 (12–16) E%, whereas PUFA intake was 4 (3–4) E%. The study population consisted of 46% females and 54% males.

Substitution of SFA with other macronutrients

Substituting 50 kcal of SFA with 50 kcal of carbohydrates showed an HR of 0.87 (95% CI: 0.74, 1.02) for HCC and 1.00 (95% CI: 0.89, 1.11) for NAFLD cirrhosis (Figure 2). Substituting SFA with fiber or

TABLE 1
Baseline characteristics of the 2 populations[1].

	HCC population	NAFLD cirrhosis population
Sex, females [*n* (%)]	36,458 (46)	35,721 (46)
Age (y)	60.0 (53.0–69.0)	60.0 (53.0–69.0)
Education, university [*n* (%)]	13,819 (17)	13,019 (17)
Current smokers [*n* (%)]	19,140 (24)	18,278 (24)
Exercise, >2 h/wk [*n* (%)]	46,077 (58)	44,523 (58)
Sleep (h/d)	7 (7–8)	7 (7–8)
Family history of CVD [*n* (%)]	8121 (10)	7833 (10)
Total energy intake (kcal)	2172 ± 735	2159 ± 731
Total food intake (g)	2649 ± 873	2624 ± 857
SFA (E%)	14 (12–16)	14 (12–16)
PUFA (E%)	4 (3–4)	4 (3–4)
Carbohydrates (E%)	51 (47–54)	51 (47–55)
Fiber (g)	25 (19–32)	25 (19–32)
Red meat (g)	41 (25–62)	40 (25–61)
Fish (g)	25 (16–38)	25 (16–38)
Butter (g)	0 (0–9)	0 (0–9)
Vegetable oil (g)	9 (0–18)	9 (0–18)
Milk (g)	149 (41–301)	149 (41–305)
Fermented milk (g)	130 (0–229)	131 (0–229)

n = 77,059 with 566 cases for the NAFLD cirrhosis population and n = 79,729 with 205 cases for the HCC population. Both populations are derived from the same pooled cohort sample, albeit with additional exclusion criteria applied to the NAFLD cirrhosis population.
Abbreviations: CVD, cardiovascular disease; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease.
[1] Data are presented as means ± SD or medians (Q3−Q1) for continuous variables and counts and percentages for categorical variables.

PUFA was not associated with HCC [HR: 0.92 (95% CI: 0.72, 1.18) and 1.09 (95% CI: 0.76, 1.57), respectively] or NAFLD cirrhosis [HR: 0.97 (95% CI: 0.82, 1.14) and 1.17 (95% CI: 0.93, 1.49), respectively] (Figure 2).

Substitution of SFA-rich foods with other foods

Substituting 100 g of milk with 100 g of fermented milk showed an HR of 0.93 (95% CI: 0.85, 1.01) for HCC (Figure 2). The HR for the substitution of milk with fermented milk and NAFLD cirrhosis was 0.97 (95% CI: 0.92, 1.03), whereas the HR for the substitution of 5 g of butter with 5 g of margarine and vegetable oil and NAFLD cirrhosis was 1.03 (95% CI: 0.99, 1.07). The latter substitution showed an HR of 1.00 (95% CI: 0.95, 1.06) for HCC (Figure 2). Substituting unprocessed red meat with fish was not associated with either HCC or NAFLD cirrhosis [HR: 1.05 (95% CI: 0.84, 1.30) and HR: 1.07 (95% CI: 0.94, 1.23), respectively] (Figure 2).

Sensitivity analyses

Findings from the primary analyses were robust in complete-case analyses and when excluding the first 2 y of follow-up (Supplemental Figures 2 and 3). Some minor deviations were observed in the complete-case analyses for the substitution of SFA with PUFA and HCC and NAFLD cirrhosis as well as for the substitution of SFA with fiber and HCC. Results were near identical for both outcomes when further subcategorization of other foods was done in the substitution models (data not shown).

When only counting NAFLD cirrhosis cases with cardiometabolic disease at baseline, similar results were demonstrated for the substitution of SFA with carbohydrates, unprocessed red meat with fish, and milk with fermented milk. The point estimate for the substitution of SFA with PUFA was attenuated and the direction of the point estimate for the substitution of SFA with fiber went from negative to positive. The point estimate for the substitution of butter with margarine and vegetable oils was somewhat augmented (Supplemental Figure 4). Associations were robust when combining the Swedish Cancer Register, the Cause of Death Register, and the NPR to define HCC (Supplemental Figure 4).

Updating the baseline to 2009 showed a positive association for the substitution of unprocessed red meat with fish [HR: 1.22 (95% CI: 1.01, 1.48)], although this association was somewhat attenuated after adjusting for prebaseline diet [HR: 1.18 (0.97, 1.44)]. No further associations were observed. Adjusting for prebaseline diet in 1997 did not materially change the results (Supplemental Figure 5).

Discussion

In this population-based sample of middle-aged to elderly Swedish males and females, no clear associations were observed for any of the nutrient or food substitutions on either NAFLD cirrhosis or HCC. Our findings were moderately robust to several sensitivity analyses investigating selection bias, reverse causation, outcome misclassification, and confounding.

Large-scale cohort studies investigating substitutions of macronutrients on the incidence of HCC in the general population are limited. However, a study of nearly half a million individuals showed a positive association with HCC by comparing high with low consumption of SFA [HR: 1.87 (95% CI: 1.23, 2.85)] [33], somewhat in line with our finding on the substitution of SFA with carbohydrates (although accompanied with low precision and a CI covering 1). RCTs whereby the replacement of SFA with carbohydrates is of interest have shown effects on liver fat reduction, a driver of NAFLD and hence HCC [34]. Translating these findings to practical food-based recommendations is however difficult as carbohydrates may represent different foods with vastly different effects on the outcome. As an example of the latter, fruit intake has been strongly inversely associated with NAFLD, cirrhosis, and liver cancer, whereas bread consumption has not [10]. In 1997, a nationally representative survey of Swedish adult males and females was conducted (Riksmaten 97–98) whereby participants had to report their habitual dietary habits over 7 d, showing that a large proportion of carbohydrates in the Swedish diet came from bread, cereal products, potatoes, milk, sour milk, fruits, and berries as well as sweets such as ice-cream and sugar-sweetened beverages [35]. Assuming the diet of our study population resembled that of the population from Riksmaten 97–98 is a strong assumption, but may give an indication of the distribution of different foods contributing to carbohydrates in our study. In line with interventional data on liver fat, it is however likely that a potential beneficial effect of carbohydrates, in place of SFA, on HCC would be mainly driven by low-glycemic and fiber-rich carbohydrates from wholegrains and fruits [36], rather than foods high in added sugar. Unfortunately, we were unable to separate added sugars from carbohydrates, as no data was available on mono- and disaccharides from natural food sources. Because of low precision and a CI covering 1, our estimate should however be interpreted with great caution. As the underlying risk of HCC in the general population is relatively low, meta-analyzing results with similar estimands as ours (that is, the relative substitution effect of replacing an isocaloric amount of SFA with carbohydrates) would be of interest to increase statistical power [37].

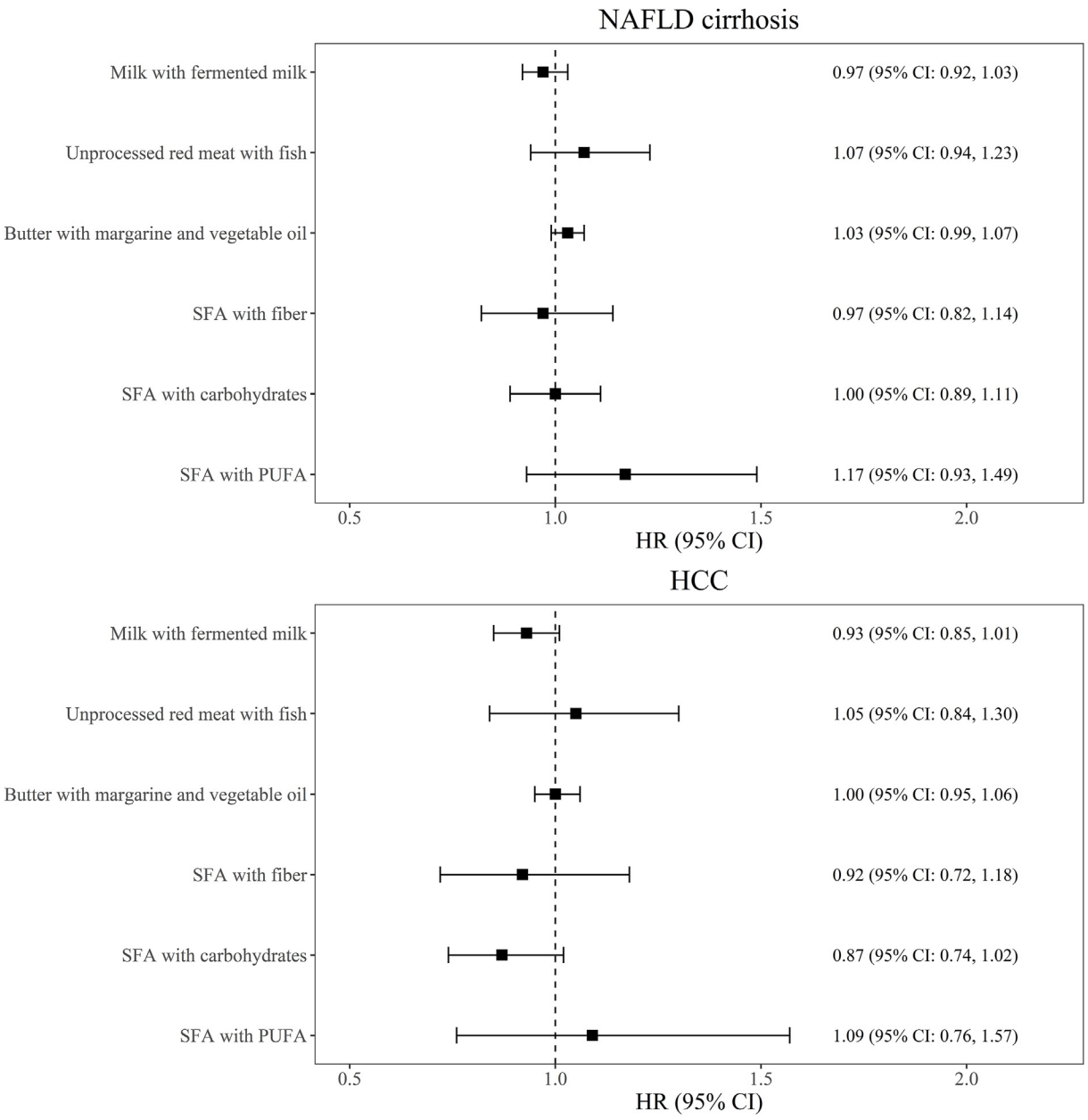

FIGURE 2. Associations between food and macronutrient substitutions and NAFLD cirrhosis and HCC. Hazard ratios (HR) with corresponding 95% confidence intervals (CI) are presented. Estimates are adjusted for age, sex, education, sleep, smoking, family history of CVD, BMI, physical activity, total energy intake (for macronutrients), total food intake (for foods), and other dietary variables necessary for estimating the joint substitution effect. The unit of exposure for each substitution is SFA with PUFA (50 kcal), SFA with carbohydrates (50 kcal), SFA with fiber (20 kcal), butter with margarine and vegetable oil (5 g), unprocessed red meat with fish (30 g), and milk with fermented milk (100 g). $n = 77{,}059$ with 566 cases for NAFLD cirrhosis and $n = 79{,}729$ with 205 cases for HCC. CVD, cardiovascular disease; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; SFA, saturated fatty acid.

Our null findings of substituting unprocessed red meat with fish on NAFLD cirrhosis are in line with some observational studies with total NAFLD as the outcome [38], but not with a recent RCT showing a reduction in liver fat of substituting red meat with fish [39]. One of many potential explanations for the discrepancies between the results from observational studies and the recent RCT may be because of the fact that individuals change food habits over time or that food characteristics themselves change over time. Updating the start of follow-up to 2009 showed similar associations for some of the food and nutrient substitutions and NAFLD cirrhosis as when the baseline was defined in 1998. Interestingly, however, the effect estimate of substituting unprocessed red meat with fish was stronger (although somewhat attenuated after prebaseline diet adjustment), lending some support to the proposed explanation of changes in food habits/characteristics over time. In addition, effect estimates of substituting SFA with PUFA and butter with margarine and vegetable oil were positive (although accompanied by a moderate degree of uncertainty with CIs covering 1) for NAFLD cirrhosis when the diet was assessed in 1997 but were attenuated when the baseline was updated to 2009. The latter may partly be explained by the removal of trans fatty acids (TFA) in most shelf-stored margarine in the mid-1990s in Sweden, although present in imported bakery margarine and other food sources for several years also in the 2000s. Likewise, the attenuation of association from substituting SFA with PUFA may also be a consequence of the

dramatic shift in TFA in foods high in PUFA in the late 1990s [40]. Lack of data on TFA intake is thus a limitation of this study. Taken together, these results indicate that findings from both RCTs as well as observational studies of dietary exposures must be interpreted within the context of when they were conducted.

Lastly, a nonstatistically significant inverse association was observed for the substitution of milk with fermented milk on HCC. This finding is interesting and corroborates previous results from observational studies of high compared with low yogurt consumption and HCC and a recent RCT where liver fat was the outcome of interest [12,41]. Potential mechanisms that may explain the inverse association with HCC may be related to a reduction in liver fat content. Compared with milk, yogurt also improves insulin resistance which is associated with less rapid progression of fibrosis in NAFLD [41,42]. Lastly, higher milk consumption may also increase circulating Insulin-like growth factor 1 (IGF-1) levels which may be implicated in the pathogenesis of HCC [43]. Findings from our study on the substitution of milk with yogurt must however be interpreted with caution as the precision of the estimate was low, as for SFA compared with carbohydrates. Synthesizing evidence from different cohorts with a similar research question would be of interest here as well.

There are several limitations of this study worth highlighting. First, as NAFLD cirrhosis lacks a formal ICD code in the Swedish NPR we had to rely on a combination of codes. This may have introduced some degree of outcome misclassification. However, most diagnoses of liver diseases have high PPV in Swedish registries [30,31]. We also excluded participants consuming >20–30 g of alcohol per day at baseline. The reason for the exclusion is that alcoholic liver disease (ALD) related cirrhosis may be misclassified as NAFLD cirrhosis if patients consume too much alcohol but are not diagnosed with ALD, leading to higher proportions of false positives. Furthermore, in sensitivity analyses we only counted cases of NAFLD cirrhosis for those who had a history of any cardiometabolic diseases or a BMI $\geq$25 kg/m^2 at baseline, demonstrating somewhat similar results as for the primary analysis. We thus believe that we may have reduced some of this potential misclassification bias. Furthermore, assuming high specificity and nondifferential sensitivity (for both outcomes), any residual misclassification bias would probably weakly bias the estimate toward the null [44]. Adding to the limitations of registry-based studies on liver cirrhosis is also the arguably high number of undiagnosed patients, as compensated cirrhosis may be asymptomatic for a long time, thereby limiting precision. Second, diet and all identified confounders were self-reported which may have led to bias from measurement error and residual confounding. As a high BMI (which is prone to bias when self-reported) may be argued to negatively influence carbohydrate consumption and positively influence HCC development, a nondifferential independent mismeasurement of BMI would probably bias the estimate of the substitution of SFA with carbohydrates downwards (using the rules of signed causal DAGs). One might, however, argue the opposite; that BMI positively influences the consumption of carbohydrates (depending on the food source), biasing the estimate upwards. Third, diet was treated as a time-fixed exposure in this study, not allowing for dietary changes to occur over time, potentially leading to exposure mismeasurement. However, as post-baseline confounders may themselves be influenced by past exposure, introducing exposure-confounding feedback, traditional regression methods are not suitable to accommodate these issues. A target trial approach whereby observational studies aim to emulate a hypothetical RCT using appropriate statistical methods would be a valid approach to employ in future studies of diet and liver disease. In addition, most time-varying analyses of diet have failed to account for confounding by past dietary exposure, possibly introducing confounding bias, although we did not observe this in our population. The latter may be because of the long time interval between the 2 dietary assessments (12 y), failing to correctly account for the confounding. Other studies have however shown similar robust results to potential confounding bias by past dietary exposure, although with similar length between dietary assessments [45,46].

A strength of this study is the use of clearly defined substitution models as an attempt to partly mimic the isocaloric conditions of a well-controlled randomized trial. Substitutions, whereby all other foods/nutrients are taken into consideration, may reduce residual confounding bias, composite variable bias, and possibly dependent measurement error imposed by traditional nutritional epidemiological approaches that adjust for total energy intake but no other foods or nutrients [15,47]. Specifying the comparator food or nutrient may also help with issues of extending study findings to other populations, as the effect estimate obtained is no longer dependent on the population-specific background distribution of the diet. One should however bear in mind that nutrients may reflect different foods over different populations, limiting the transportability of our results. Further strengths include the long-follow-up time to allow for rare outcomes such as HCC and NAFLD cirrhosis to develop, the use of prebaseline BMI as a confounder to separate temporality between BMI and diet as well as the near complete follow-up via linkage to national health registries, minimizing selection bias due to loss to follow-up.

In conclusion, no clear associations were observed between diet and NAFLD cirrhosis nor HCC. Although accompanied by low precision, findings on the substitution of SFA with carbohydrates and milk with fermented milk and HCC are interesting and need to be replicated in other cohorts and preferentially meta-analyzed to further increase statistical power.

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Author contributions

The authors' responsibilities were as follows – MF, FR, LL, UR, EWL, JV: designed research; MF: analyzed the data; MF: wrote the first draft of the manuscript; UR: had primary responsibility for final content; and all authors: read and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Data availability

Data are available from SIMPLER (www.simpler4health.se) for researchers who meet the criteria, that is, an ethical approval is demanded, for access to SIMPLER data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2024.05.018.

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