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Incident Heart Failure and Atrial Fibrillation after a Community Diagnosis of Nonalcoholic Fatty Liver Disease: A Matched Retrospective Cohort Study with Competing-Risk Analysis

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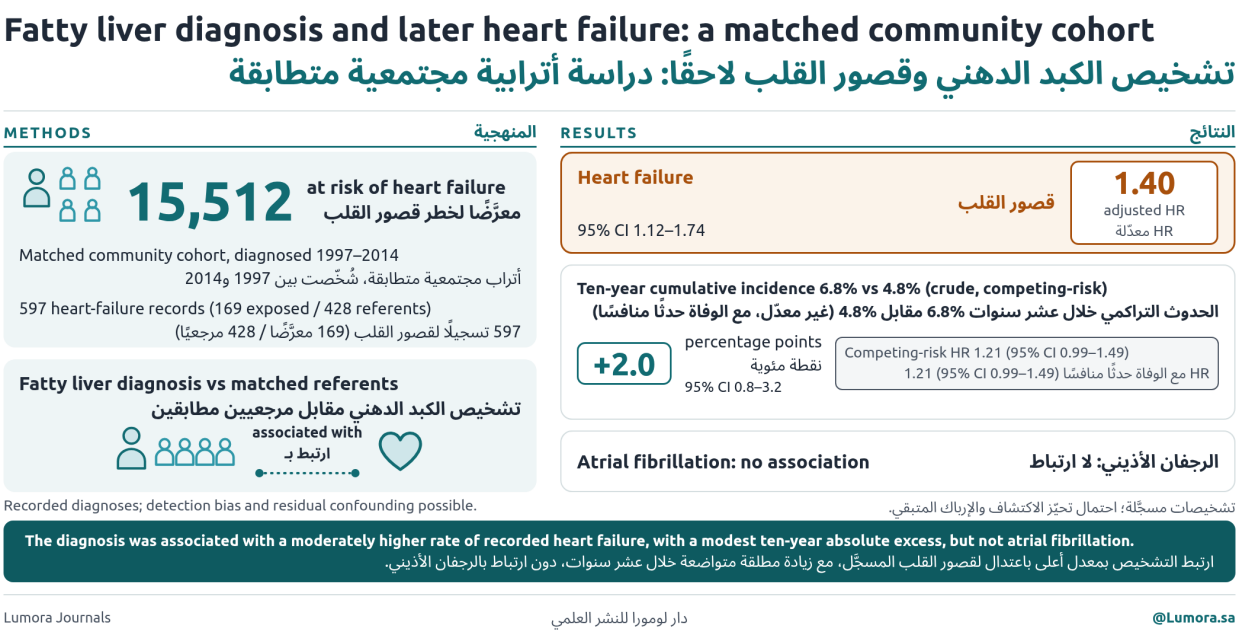
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Graphical abstract



Graphical abstract: The diagnosis was associated with a moderately higher rate of recorded heart failure, with a modest ten-year absolute excess, but not atrial fibrillation. Designed by the Lumora Journals production team using hand-coded HTML/SVG rendered in Google Chrome.

Abstract

Background/Objectives: Heart failure and atrial fibrillation are studied far less often than ischaemic endpoints in nonalcoholic fatty liver disease, and published cohorts censor deaths rather than modelling them. We estimated the association with incident heart failure.

Methods: In a county records-linkage population, adults first diagnosed in 1997-2014 were matched on age and sex to up to four referents sharing their index date. A first heart-failure record was analysed by Cox regression stratified on matched set and adjusted for index-date cardiometabolic conditions, and by Fine-Gray and Aalen-Johansen estimators with death as competing event.

Results: Among 15,512 subjects at risk, 597 records accrued. The adjusted hazard ratio was 1.40 (95% CI 1.12–1.74), the sub-distribution hazard ratio 1.21 (95% CI 0.99–1.49), and ten-year cumulative incidence 2.0 (95% CI 0.8–3.2) percentage points higher in exposed subjects. The relative association appeared larger in those without a recorded cardiometabolic condition (interaction p = 0.005), an estimate based on few events, and attenuated after adjustment for imputed body-mass index. Atrial fibrillation showed no adjusted association (1.01 (95% CI 0.81–1.26)).

Conclusions: The diagnosis was associated with a moderately higher rate of recorded heart failure but not atrial fibrillation; the absolute ten-year excess was modest, and shared adiposity and differential clinical attention remain plausible explanations.

Keywords: non-alcoholic fatty liver disease; metabolic dysfunction-associated steatotic liver disease; heart failure; atrial fibrillation; cohort studies; competing risks; cumulative incidence; medical record linkage

1. Introduction

Nonalcoholic fatty liver disease, renamed metabolic dysfunction-associated steatotic liver disease in 2023 [1], is the commonest chronic liver condition in high-income countries and is defined by hepatic steatosis in

the presence of cardiometabolic risk factors. Only a minority of affected adults progress to cirrhosis, and most of the excess illness they experience is cardiovascular and metabolic rather than hepatic [2,3]. A large share of adults with cardiometabolic risk factors also carry undetected liver fibrosis, so the condition is both common and under-recognised [4]. Understanding which cardiovascular endpoints are affected, and by how much in absolute terms, therefore matters more for the care of these patients than the hepatic prognosis that dominates specialist practice.

The cardiovascular literature in this field has concentrated on ischaemic endpoints. A nationwide histology-based cohort and a meta-analysis of published cohorts report higher rates of fatal and non-fatal cardiovascular events, including myocardial infarction and stroke, among affected adults [3,5], although in a matched primary-care record cohort of 18 million European adults the association with acute myocardial infarction and stroke was largely explained by established cardiovascular risk factors [6], and the community cohort analysed here has previously been examined for sex differences in ischaemic events [7]. Heart failure and atrial fibrillation have received much less attention despite being mechanistically plausible consequences of the same metabolic and inflammatory state, and despite generating recurrent hospital admission rather than a single event. Meta-analyses of the available cohorts report pooled relative risks of about 1.4 for both endpoints, with substantial heterogeneity and with most of the association for atrial fibrillation attributable to co-existing cardiometabolic risk factors [8,9]. One large histology-based cohort reported an adjusted hazard ratio near 1.75 for congestive heart failure [3], and one nationwide study of young adults found a graded association with atrial fibrillation using a laboratory-derived index rather than a recorded diagnosis [10]. In the same community and records system as ours, incident heart failure has been examined for other exposures with comparable matched designs [11,12].

Two features of this evidence limit its use at the bedside. First, almost every published cohort treats death as a censoring event rather than as a competing event, even though affected adults die substantially more often than comparators [2]; a hazard ratio estimated in that way describes the rate among survivors and cannot be translated into the probability that a patient will develop the outcome [13]. Second, absolute risks are rarely reported at all, so a clinician cannot convert a relative estimate into an expected number of events over a clinically meaningful horizon. A third, subtler problem is that studies which match at design frequently discard the matching at analysis, and studies which use routinely recorded diagnoses rarely examine whether greater clinical attention among exposed subjects inflates outcome detection.

We therefore analysed a community cohort in which every subject with a first recorded diagnosis of fatty liver disease was matched on age and sex to up to four general-population referents sharing the same index date, and estimated the association with a first heart-failure record, with death before heart failure treated as a competing event throughout. Atrial fibrillation, a combined cardiac endpoint and ischaemic cardiovascular events were examined as secondary outcomes, incident diabetes served as a positive comparator against which outcome ascertainment could be judged, and absolute cumulative incidence and risk differences were reported alongside every relative estimate. We hypothesised that adjustment for cardiometabolic conditions present at the index date would attenuate but not remove the association, and that the relative association would be larger among subjects with no such condition recorded.

2. Materials and Methods

The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement for cohort studies [14] and, because the cohort was assembled from routinely recorded health data, with the extension for such data [15].

2.1. Study Design and Data Source

This was a matched retrospective cohort study. The source population comprised all adult residents of a single United States county, served by a medical-record-linkage system that captures essentially the whole resident population, in whom a first diagnosis of nonalcoholic fatty liver disease was recorded between 1997 and 2014. Each such subject formed the index member of a matched set together with up to four general-population referents of the same age and sex drawn from the same community and assigned the same index date. Follow-up ran through the records system to death or last recorded contact. The cohort and its assembly are described in the source report of the study population [2].

The analysis used the publicly released version of these data, distributed as three linked tables with version 3.8-12 of the survival analysis package for the R environment [16]: a baseline table with one record per subject, a longitudinal table of recorded measurements, and a table of dated outcome records. In the released version all calendar dates have been replaced by intervals in days from the index date, ages are integer years at the index date, subject identifiers are arbitrary integers, and a random ten per cent of subjects has been withheld. Estimates therefore are not expected to reproduce the source report exactly, and no re-identification was attempted.

2.2. Participants, Index Date and Follow-Up

Exposure was fixed at time zero: a subject was classified as exposed only if they were the index member of their matched set, that is, the subject whose identifier equals the matched-set identifier, and carried a diagnosis dated at or before day zero. Matched sets were removed in full, in this order, (i) when their index member was absent from the public release; (ii) when their index member appeared in the release with a different matched-set identifier, because they had first served as a comparator for an earlier case; and (iii) when their index member had no diagnosis dated at or before day zero. Every retained set therefore contained an exposed subject at time zero. Adults aged 18 years or older with a positive follow-up interval and a recorded vital status were retained; in the release these criteria removed no further subject. Applied to the release distributed with version 3.8-12 of the package, these rules give 16,271 subjects in 3,518 sets; applied to the earlier release distributed with version 3.5-8 they give 16,253 subjects in 3,514 sets, because that release lacks the matched-set identifier for 31 index members and dates some diagnosis records differently (Supplementary Material S1).

Follow-up began at the index date for exposed and referent subjects alike, so that no interval of guaranteed event-free time was assigned to either group. Any outcome record dated at or before day zero defined prevalent disease and removed that subject from the corresponding risk set rather than counting as an event; consequently the analysed population differs slightly between outcomes. The assembly of the cohort, with the number of subjects remaining at each step, is shown in Figure 1.

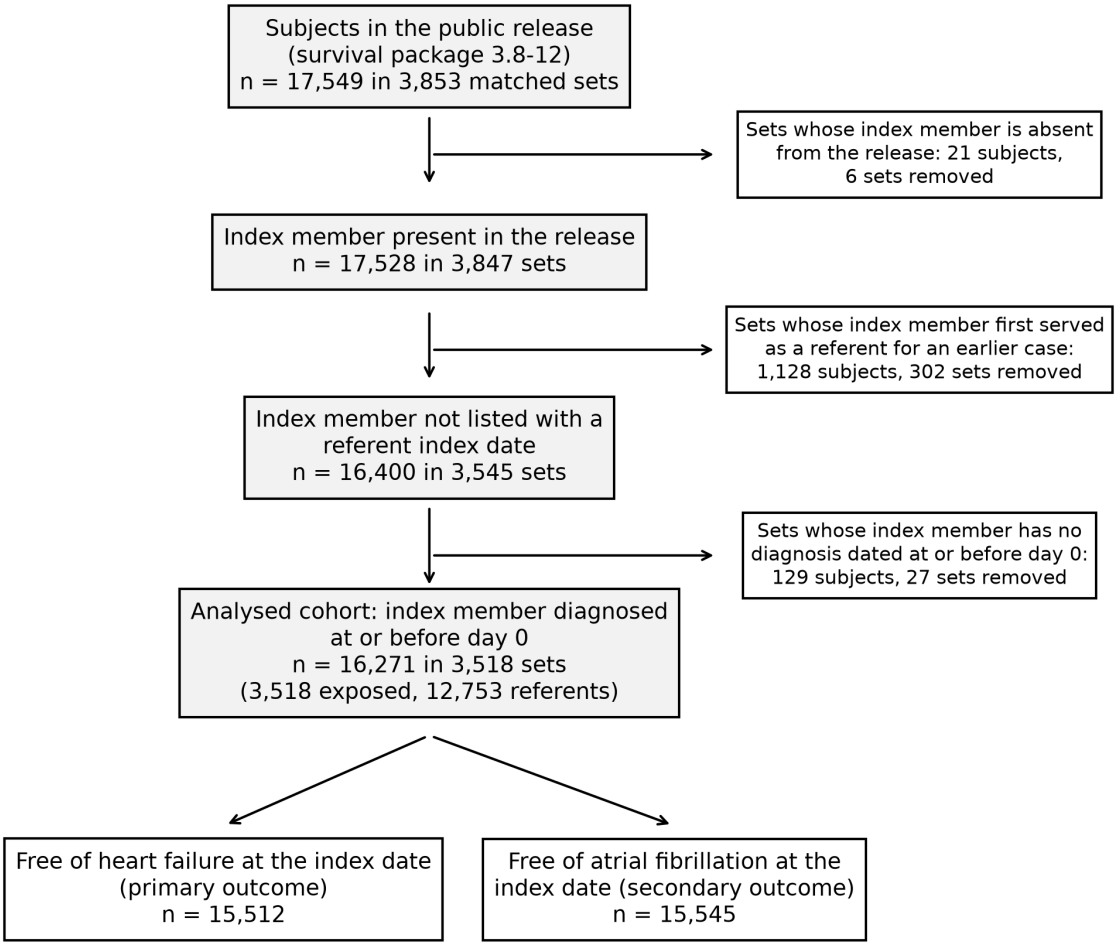


Figure 1. Assembly of the matched cohort from the public release of the community fatty liver disease cohort.

Counts are subjects (matched sets) remaining after each step. Exposed subjects and their matched referents are removed together whenever a matched set is excluded, so the matching structure is preserved. The age, follow-up and vital-status criteria removed no subject and are therefore not shown as a separate step. The last two boxes give the numbers analysed for the primary and the first secondary outcome; subjects with the outcome recorded at or before the index date are excluded from that outcome only.

A minority of referents had their own diagnosis recorded during follow-up. These subjects were retained as unexposed in the primary analysis, which therefore estimates the association of a diagnosis present at time zero, and were censored at the date of their own diagnosis in a sensitivity analysis.

2.3. Variables

The primary outcome was the first heart-failure record dated after the index date. Secondary outcomes were the first atrial-fibrillation record; the earlier of a heart-failure or atrial-fibrillation record; the first ischaemic cardiovascular event, defined as myocardial infarction, an angina or ischaemia record, stroke or cardiac arrest; and, as a positive comparator chosen because a strong association is already established in this population [2], the first record of diabetes mellitus. Death from any cause was the competing event and was also reported in its own right. All outcomes were those recorded in routine care, without central adjudication.

Confounders were selected from a directed acyclic graph in which adiposity and insulin resistance are common causes of both the hepatic phenotype and the cardiac outcomes (Figure S4). Age and sex were controlled by the matched design and by stratification on matched set. Diabetes mellitus, hypertension, dyslipidaemia and ischaemic cardiovascular disease recorded at or before the index date entered the main adjusted model because each precedes time zero and each is a plausible common cause; for the ischaemic and diabetes outcomes the corresponding condition is an exclusion criterion and was therefore omitted from the covariate set. Body-mass index was taken from the baseline table, and high-density lipoprotein cholesterol as the last value recorded in the two years ending at the index date. No variable measured after the index date was adjusted for.

Continuous variables were handled as follows. Age entered the primary analysis only through the matching and the matched-set strata, and appeared as a penalised spline in the unstratified specification. Body-mass index was categorised at conventional thresholds for description and entered as a continuous variable in the multiply imputed model; high-density lipoprotein cholesterol was kept continuous throughout. The diagnosis itself was ascertained in the source cohort by a code-based algorithm whose validity was checked against medical records [7]; the underlying code lists are held by the data custodians and are not part of the public release, whereas every derivation rule applied here is published with this article.

Three record-derived variables were not usable. Systolic and diastolic blood pressure and smoking status were recorded for a small minority of subjects and are described only. Every value labelled total cholesterol in the released measurement table duplicated the high-density lipoprotein value for the same subject on the same day (159,647 of 159,647 same-day pairs) and followed the distribution of the latter, so that series was judged to carry no independent information and was excluded; the check is documented with the derived data. The fibrosis-4 index was not used: a value recorded in the two years ending at the index date was available for 671 subjects (4.1%), 358 exposed (10.2%) and 313 referents (2.5%), too few and too unevenly recorded to support adjustment or an analysis by fibrosis category.

2.4. Statistical Analysis

No target sample size was set: the number of subjects and the length of follow-up were fixed by the released cohort, and the precision actually achieved is described by the confidence intervals reported below rather than by a power calculation. The primary analysis was a cause-specific Cox proportional-hazards regression of time from the index date to a first heart-failure record, stratified by matched set so that age and sex were controlled by the matching, adjusted for the four index-date conditions and fitted with the Efron approximation for ties (Model 2). Model 1 was stratified only. A third specification replaced the matched-set strata by age and sex as covariates with a robust variance clustered on matched set, so that a directly comparable Fine-Gray sub-distribution model could be fitted with the same covariates and death before the outcome as the competing event [13]. Absolute risk was estimated by the Aalen-Johansen estimator at five and ten years in each group, with the difference between groups, an independence-based interval and a percentile interval from 1,000 bootstrap resamples of whole matched sets, which preserves the dependence created by matching; crude incidence rates per 1000 person-years were computed with exact Poisson limits.

Effect modification was examined by likelihood-ratio interaction tests and stratum-specific estimates in four subgroups: cardiometabolic burden at the index date, sex, age group and freedom from any recorded cardiovascular disease. Sensitivity analyses were the unstratified model just described, propensity-score overlap weighting on age, sex and the four index-date conditions, exclusion of heart-failure records arising

in the first twelve months, censoring of referents at their own later diagnosis, restriction to subjects free of recorded cardiovascular disease, and a fully adjusted model adding body-mass index and high-density lipoprotein cholesterol after multiple imputation by chained equations with ten imputations, the cumulative hazard included in the imputation model and estimates combined by Rubin's rules. Covariate balance was summarised by standardised mean differences before and after weighting. The minimum strength of association that an unmeasured common cause would need with both exposure and outcome in order to account for the primary estimate was expressed as an E-value [17].

Proportional hazards were assessed by scaled Schoenfeld residuals with per-covariate and global tests and a residual plot (Figure S2), and by adding an interaction with the logarithm of follow-up time for any covariate whose test suggested departure. Effect estimates are reported as hazard ratios with 95% confidence intervals and two-sided p values to three decimal places. One primary outcome, one primary model and one primary contrast were specified and no adjustment for multiplicity was applied to them; all other comparisons are secondary or supportive, are reported without adjustment and are interpreted as descriptive. Analyses used R 4.3.3 with the survival package for the regression, competing-risk and cumulative-incidence models, mice 3.16.0 for imputation and cmprsk 2.2.11 for competing-risk estimation, and Python 3.11 with pandas, numpy, statsmodels and lifelines 0.30.3 for descriptive statistics and the propensity-score analysis; the data were those distributed with version 3.8-12 of the survival package. The matched-set bootstrap, the per-covariate proportional-hazards tests and the time-varying terms additionally reported were computed in Python 3.13 with numpy 2.5, scipy 1.18, pandas 2.3, statsmodels 0.15 and pyreadr 0.5; the code and the derived analysis file are provided as Supplementary Material S1.

2.5. Reporting, Ethics and Availability

The analysis used publicly available, de-identified data from which all calendar dates had been removed. The original cohort was assembled under institutional review board approval at the contributing institutions with the research authorisation of participants, as described in the source report [2]. The study was not registered.

3. Results

Results are presented in the following order: the assembled cohort and its characteristics at the index date, then follow-up, event counts and absolute risk, then the relative associations, then the sensitivity and subgroup analyses.

3.1. Cohort and Characteristics at the Index Date

The public release contained 17,549 subjects. After removal of matched sets whose index member was absent, appeared with another matched-set identifier or had no diagnosis dated at or before day zero, 16,271 subjects remained in 3,518 matched sets, of whom 3,518 were exposed and 12,753 were matched referents, a mean of 4.63 subjects per set (Figure 1). The median age at the index date was 52 years and 53.3% were women.

Characteristics at the index date are given in Table 1. Age and sex were balanced by design, but exposed subjects carried a substantially heavier cardiometabolic load: diabetes mellitus had been recorded in 28.2% of them compared with 9.6% of referents, hypertension in 44.3% compared with 23.8%, and dyslipidaemia in 71.3% compared with 42.9%. The largest standardised difference of any characteristic was 0.778, for body-mass index, and among the characteristics entered into the weighting model the largest was 0.599;

propensity-score overlap weighting removed the latter imbalance entirely, leaving a largest standardised difference of 0.000 among those characteristics while body-mass index and high-density lipoprotein cholesterol, which were not in the weighting model, remained imbalanced at up to 0.548 (Figure 2). Body-mass index was not recorded for 27.9% of subjects overall and the shortfall was differential, affecting 31.5% of referents but only 14.9% of exposed subjects; high-density lipoprotein cholesterol was missing for 42.7%, blood pressure for 86.8% and smoking status for 95.4%.

Table 1. Characteristics at the index date of adults with a recorded diagnosis of nonalcoholic fatty liver disease and their age- and sex-matched referents.

Characteristic	Overall (n = 16,271)	Fatty liver disease (n = 3,518)	Referent (n = 12,753)
Age at the index date, years, mean (SD)	52.2 (14.8)	51.9 (14.9)	52.3 (14.8)
Age group, years, n (%)			
18–44	4,984 (30.6)	1,120 (31.8)	3,864 (30.3)
45–64	7,839 (48.2)	1,673 (47.6)	6,166 (48.3)
65+	3,448 (21.2)	725 (20.6)	2,723 (21.4)
Sex, n (%)			
Women	8,671 (53.3)	1,851 (52.6)	6,820 (53.5)
Men	7,600 (46.7)	1,667 (47.4)	5,933 (46.5)
Body-mass index, kg/m2, mean (SD)	30.1 (7.1)	34.2 (7.6)	28.7 (6.4)
Body-mass index category, kg/m2, n (%)			
<25	2,815 (24.0)	218 (7.3)	2,597 (29.7)
25–29.9	3,777 (32.2)	703 (23.5)	3,074 (35.2)
30–34.9	2,673 (22.8)	896 (29.9)	1,777 (20.3)
35+	2,461 (21.0)	1,176 (39.3)	1,285 (14.7)
Diabetes mellitus at the index date, n (%)	2,222 (13.7)	992 (28.2)	1,230 (9.6)
Hypertension at the index date, n (%)	4,591 (28.2)	1,557 (44.3)	3,034 (23.8)
Dyslipidaemia at the index date, n (%)	7,975 (49.0)	2,507 (71.3)	5,468 (42.9)
Number of cardiometabolic conditions, n (%)			
None recorded	7,362 (45.2)	774 (22.0)	6,588 (51.7)

Characteristic	Overall (n = 16,271)	Fatty liver disease (n = 3,518)	Referent (n = 12,753)
One	4,496 (27.6)	1,096 (31.2)	3,400 (26.7)
Two or three	4,413 (27.1)	1,648 (46.8)	2,765 (21.7)
Ischaemic cardiovascular disease at the index date, n (%)	2,110 (13.0)	663 (18.8)	1,447 (11.3)
Heart failure at the index date, n (%)	759 (4.7)	256 (7.3)	503 (3.9)
Atrial fibrillation at the index date, n (%)	726 (4.5)	228 (6.5)	498 (3.9)
HDL cholesterol, mg/dL, mean (SD)	51.8 (16.5)	46.5 (13.9)	54.3 (17.0)
Systolic blood pressure, mm Hg, mean (SD)	132.0 (19.9)	132.5 (19.3)	131.7 (20.2)
Recorded smoking status, n (%)			
Never	493 (65.7)	185 (65.1)	308 (66.1)
Current or former	257 (34.3)	99 (34.9)	158 (33.9)
Follow-up, years, mean (SD)	6.7 (4.3)	6.6 (4.3)	6.7 (4.4)

Values are numbers (percentages) for categorical and binary variables and means (standard deviations) for continuous variables; percentages for body-mass index category and smoking status use subjects with a recorded value as denominator. Body-mass index, cholesterol, blood pressure and smoking were recorded for a subset of subjects and the denominators differ; the proportion recorded for each is given in Section 3.1. Cardiometabolic conditions are those with a record dated at or before the index date. HDL, high-density lipoprotein.

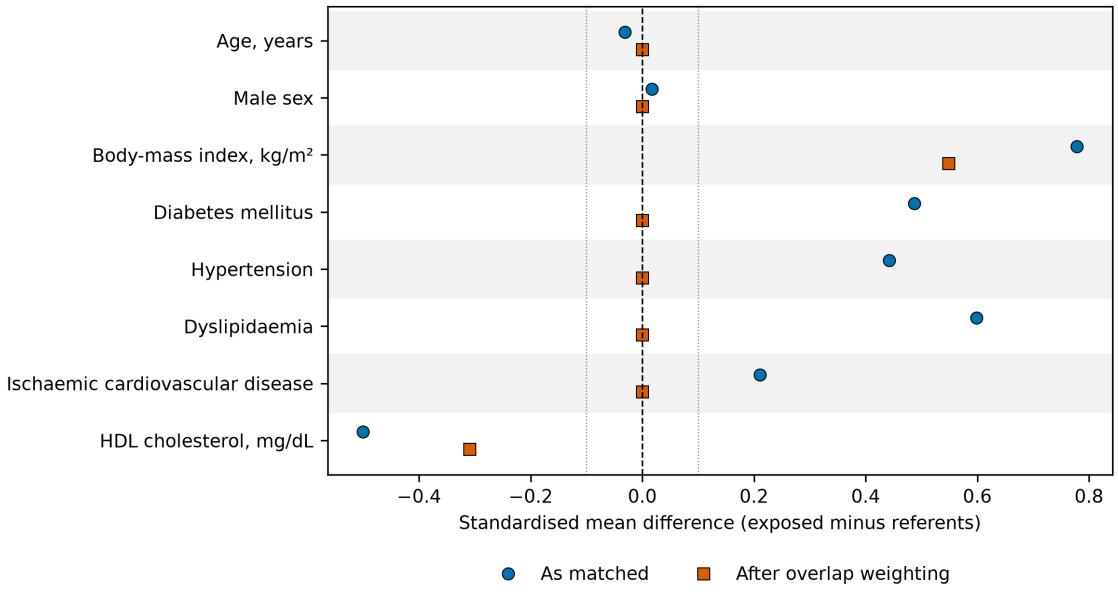


Figure 2. Standardised mean differences between subjects with fatty liver disease and their matched referents for characteristics recorded at the index date, as matched and after propensity-score overlap weighting.

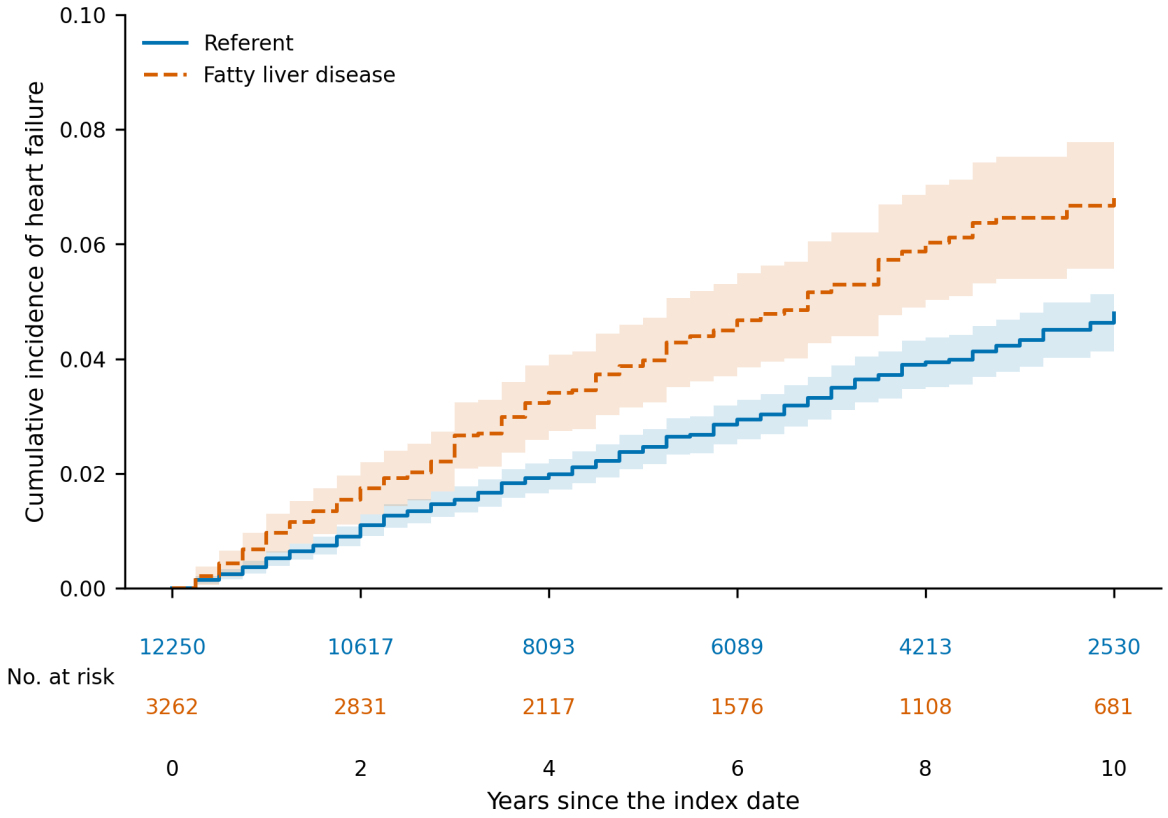
A standardised mean difference of zero indicates identical distributions; values within 0.1 of zero are conventionally regarded as negligible imbalance. Each marker is a point summary and carries no interval, so no uncertainty is displayed. Age and sex were matching variables; body-mass index and high-density

lipoprotein cholesterol were not in the weighting model and are shown for subjects in whom they were recorded.

3.2. Follow-Up, Events and Absolute Risk

The cohort accrued 109,154 person-years of follow-up, with a median of 6.0 years (25th to 75th percentile 3.2 to 9.3, maximum 19.9). 1,286 subjects died during follow-up, and cumulative mortality at ten years was 13.7% (95% CI 12.1–15.3) among exposed subjects compared with 10.3% (95% CI 9.5–11.1) among referents (Figure S3), so death was a materially more frequent competing event in the exposed group.

15,512 subjects were free of heart failure at the index date and 597 incident records accrued, 169 among exposed subjects and 428 among referents. The crude incidence was 7.9 (95% CI 6.7–9.2) per thousand person-years among exposed subjects and 5.3 (95% CI 4.8–5.8) per thousand person-years among referents. Cumulative incidence with death treated as a competing event reached 6.8% (95% CI 5.7–7.9) and 4.8% (95% CI 4.3–5.3) respectively at ten years, a difference of 2.0 (95% CI 0.8–3.2) percentage points; at five years the corresponding values were 4.0% (95% CI 3.2–4.7) and 2.5% (95% CI 2.2–2.8), a difference of 1.5 (95% CI 0.7–2.3) percentage points. Percentile intervals from a bootstrap of whole matched sets were almost identical: 0.8–3.3 percentage points at ten years and 0.8–2.3 at five years (Supplementary Table S1). The curves separated within the first two years and continued to diverge (Figure 3). Counts, rates and cumulative incidence for every outcome are given in Table 2.



Abbreviations and symbols: CI, confidence interval.

Figure 3. Cumulative incidence of a first heart-failure record by exposure group, with death before heart failure treated as a competing event.

Aalen-Johansen estimates with shaded 95% confidence bands; the numbers below the axis are subjects still at risk. The curves are crude, that is, they are not adjusted for conditions recorded at the index date.

Table 2. Events, crude incidence and cumulative incidence at 10 years by outcome and exposure group.

Outcome	At risk	Events (exposed / referents)	Rate per 1000 person-years, exposed	Rate per 1000 person-years, referents	10-year cumulative incidence, exposed	10-year cumulative incidence, referents	Difference, percentage points
Heart failure	15,512	169 / 428	7.9 (95% CI 6.7–9.2)	5.3 (95% CI 4.8–5.8)	6.8% (95% CI 5.7–7.9)	4.8% (95% CI 4.3–5.3)	2.0 (95% CI 0.8–3.2)
Atrial fibrillation	15,545	141 / 465	6.5 (95% CI 5.5–7.7)	5.7 (95% CI 5.2–6.3)	5.9% (95% CI 4.8–6.9)	5.5% (95% CI 4.9–6.1)	0.4 (95% CI −0.8 to 1.6)
Heart failure or atrial fibrillation	15,063	220 / 608	10.8 (95% CI 9.4–12.3)	7.8 (95% CI 7.2–8.4)	9.3% (95% CI 8.0–10.6)	7.4% (95% CI 6.8–8.1)	1.9 (95% CI 0.4–3.4)
Ischaemic cardiovascular events	14,161	271 / 692	15.0 (95% CI 13.3–16.9)	9.4 (95% CI 8.8–10.2)	13.3% (95% CI 11.6–15.0)	8.4% (95% CI 7.7–9.1)	4.9 (95% CI 3.1–6.7)
Diabetes mellitus	14,049	382 / 602	25.4 (95% CI 22.9–28.1)	8.0 (95% CI 7.3–8.6)	20.0% (95% CI 17.9–22.0)	7.1% (95% CI 6.4–7.7)	12.9 (95% CI 10.7–15.1)

Abbreviations and symbols: CI, confidence interval.

Subjects with the outcome recorded at or before the index date are excluded from that row. Rates are crude, with exact Poisson intervals. Cumulative incidence is the Aalen-Johansen estimate with death before the outcome as the competing state; the difference is exposed minus referents with an independence-based interval; intervals from a bootstrap of whole matched sets are given in Supplementary Table S1. Diabetes mellitus is a positive-comparator outcome.

For atrial fibrillation, 606 incident records accrued among 15,545 subjects at risk, and ten-year cumulative incidence was 5.9% (95% CI 4.8–6.9) among exposed subjects compared with 5.5% (95% CI 4.9–6.1) among referents, a difference of 0.4 (95% CI −0.8 to 1.6) percentage points (Figure S1). Ischaemic cardiovascular events were commoner and more clearly separated, with 963 records and a ten-year risk difference of 4.9 (95% CI 3.1–6.7) percentage points; the positive-comparator diabetes outcome showed the largest separation of all, with a ten-year risk difference of 12.9 (95% CI 10.7–15.1) percentage points.

3.3. Relative Associations

Hazard ratios for every outcome and model are given in Table 3 and displayed in Figure 4. With stratification on matched set alone, the outcome-specific hazard ratio for heart failure was 1.80 (95% CI 1.48–2.19). After adjustment for the four conditions recorded at the index date, the primary estimate was 1.40 (95% CI 1.12–1.74) with a two-sided p value of p = 0.003 and a likelihood-ratio p value of p = 0.003, based on 597 events and 119.4 events per adjusted parameter. Replacing the matched-set strata by age and sex as covariates gave 1.25 (95% CI 1.03–1.52), and the sub-distribution model with the same covariates and death as the competing event gave 1.21 (95% CI 0.99–1.49).

Table 3. Hazard ratios for each outcome comparing subjects with fatty liver disease with their matched referents.

Outcome	Model	Hazard ratio (95% CI)	p-value
Heart failure	Model 1 (matched sets only)	1.80 (95% CI 1.48–2.19)	p < 0.001
Heart failure	Model 2 (+ index-date cardiometabolic conditions)	1.40 (95% CI 1.12–1.74)	p = 0.003

Outcome	Model	Hazard ratio (95% CI)	p-value
Heart failure	Model 2 without matched-set stratification (age and sex as covariates)	1.25 (95% CI 1.03–1.52)	p = 0.025
Heart failure	Sub-distribution model (Fine-Gray), Model 2 covariates without stratification	1.21 (95% CI 0.99–1.49)	p = 0.06
Atrial fibrillation	Model 1 (matched sets only)	1.32 (95% CI 1.08–1.62)	p = 0.007
Atrial fibrillation	Model 2 (+ index-date cardiometabolic conditions)	1.01 (95% CI 0.81–1.26)	p = 0.93
Atrial fibrillation	Model 2 without matched-set stratification (age and sex as covariates)	1.03 (95% CI 0.84–1.26)	p = 0.78
Atrial fibrillation	Sub-distribution model (Fine-Gray), Model 2 covariates without stratification	0.99 (95% CI 0.81–1.22)	p = 0.95
Heart failure or atrial fibrillation	Model 1 (matched sets only)	1.71 (95% CI 1.44–2.03)	p < 0.001
Heart failure or atrial fibrillation	Model 2 (+ index-date cardiometabolic conditions)	1.30 (95% CI 1.08–1.57)	p = 0.006
Heart failure or atrial fibrillation	Model 2 without matched-set stratification (age and sex as covariates)	1.23 (95% CI 1.04–1.45)	p = 0.015
Heart failure or atrial fibrillation	Sub-distribution model (Fine-Gray), Model 2 covariates without stratification	1.20 (95% CI 1.01–1.42)	p = 0.038
Ischaemic cardiovascular events	Model 1 (matched sets only)	1.72 (95% CI 1.47–2.01)	p < 0.001
Ischaemic cardiovascular events	Model 2 (+ index-date cardiometabolic conditions)	1.29 (95% CI 1.09–1.53)	p = 0.003
Ischaemic cardiovascular events	Model 2 without matched-set stratification (age and sex as covariates)	1.43 (95% CI 1.22–1.67)	p < 0.001
Ischaemic cardiovascular events	Sub-distribution model (Fine-Gray), Model 2 covariates without stratification	1.38 (95% CI 1.18–1.61)	p < 0.001
Diabetes mellitus	Model 1 (matched sets only)	3.38 (95% CI 2.92–3.93)	p < 0.001
Diabetes mellitus	Model 2 (+ index-date cardiometabolic conditions)	2.84 (95% CI 2.43–3.32)	p < 0.001
Diabetes mellitus	Model 2 without matched-set stratification (age and sex as covariates)	2.79 (95% CI 2.41–3.22)	p < 0.001

Outcome	Model	Hazard ratio (95% CI)	p-value
Diabetes mellitus	Sub-distribution model (Fine-Gray), Model 2 covariates without stratification	2.69 (95% CI 2.34–3.10)	p < 0.001

Model 1 is stratified by matched set only, so age and sex are controlled by the matching. Model 2 adds diabetes, hypertension, dyslipidaemia and ischaemic cardiovascular disease recorded at or before the index date; for the ischaemic and diabetes outcomes the corresponding condition is an exclusion criterion and is therefore omitted from the covariate set. The unstratified model replaces the matched-set strata with age and sex as covariates and uses a robust variance clustered on matched set. The sub-distribution model uses the unstratified covariate set with death before the outcome treated as a competing event, so it is directly comparable with the unstratified cause-specific estimate. CI, confidence interval.

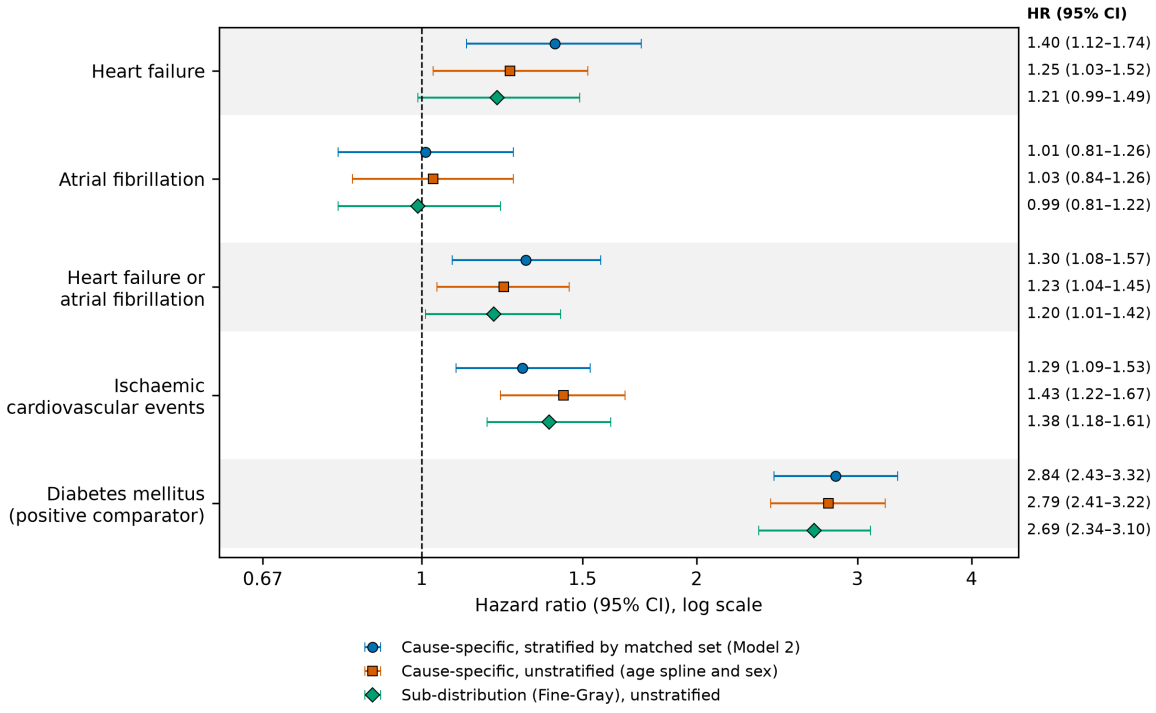


Figure 4. Cause-specific and sub-distribution hazard ratios for each outcome, comparing subjects with fatty liver disease with their matched referents; the unstratified cause-specific model is also shown, as in the legend.

Cause-specific models are stratified by matched set and adjusted for diabetes, hypertension, dyslipidaemia and ischaemic cardiovascular disease recorded at or before the index date; sub-distribution models use the same covariates with death before the outcome as the competing event. Diabetes mellitus is a positive-comparator outcome included to show how outcome ascertainment behaves. HR, hazard ratio; CI, confidence interval.

For atrial fibrillation the association present with stratification alone (1.32 (95% CI 1.08–1.62)) disappeared after adjustment (1.01 (95% CI 0.81–1.26)), and the sub-distribution estimate agreed (0.99 (95% CI 0.81–1.22)). The combined cardiac endpoint gave 1.30 (95% CI 1.08–1.57) after adjustment (sub-distribution 1.20 (95% CI 1.01–1.42)); because every heart-failure record also counts towards it and atrial fibrillation showed no adjusted association, this estimate largely restates the heart-failure finding rather than adding independent evidence. Ischaemic cardiovascular events retained an association after adjustment (1.29 (95% CI 1.09–1.53), sub-distribution 1.38 (95% CI 1.18–1.61)), and the positive-comparator diabetes outcome remained strongly associated (2.84 (95% CI 2.43–3.32)), which indicates that outcome ascertainment in these data behaves as expected where a large association is known to exist.

The scaled Schoenfeld test gave no evidence against proportional hazards for the exposure term of the primary model (p = 0.33), although the global test was borderline (p = 0.031); the residual plot showed no systematic drift over follow-up (Figure S2). The global result was driven by diabetes recorded at the index date (p = 0.014; p ≥ 0.13 for the other covariates). Allowing the diabetes coefficient to change with the logarithm of follow-up time gave a primary estimate of 1.36 (95% CI 1.09–1.70), and an exposure-by-log-time term was not supported (p = 0.38).

3.4. Sensitivity Analyses

Sensitivity analyses are given in Table 4. Discarding the matching and modelling age and sex as covariates gave 1.25 (95% CI 1.03–1.52), and propensity-score overlap weighting gave 1.21 (95% CI 1.00–1.47). Excluding heart-failure records arising in the first twelve months gave 1.28 (95% CI 1.01–1.64). Censoring the 264 referents whose own diagnosis was recorded during follow-up left the estimate essentially unchanged at 1.41 (95% CI 1.14–1.76). Restriction to subjects free of any recorded cardiovascular disease at the index date gave a larger estimate, 1.69 (95% CI 1.24–2.31).

Table 4. Sensitivity and subgroup analyses for incident heart failure.

Analysis	Specification	Hazard ratio (95% CI)	p-value
Sensitivity	Matching discarded: age spline and sex as covariates, robust variance clustered on matched set	1.25 (95% CI 1.03–1.52)	p = 0.025
Sensitivity	Propensity-score overlap weighting instead of matching	1.21 (95% CI 1.00–1.47)	p = 0.05
Sensitivity	Excluding heart failure recorded in the first 12 months (503 events)	1.28 (95% CI 1.01–1.64)	p = 0.045
Sensitivity	Referents censored when their own diagnosis is recorded	1.41 (95% CI 1.14–1.76)	p = 0.002
Sensitivity	Restricted to subjects free of recorded cardiovascular disease at the index date	1.69 (95% CI 1.24–2.31)	p < 0.001
Sensitivity	Model 3: body-mass index and HDL cholesterol added after multiple imputation (m = 10)	1.17 (95% CI 0.93–1.48)	p = 0.18
Unmeasured confounding	E-value for the point estimate and for the confidence limit closest to the null	2.15 / 1.50	
Subgroup: Cardiometabolic burden at the index date	No recorded condition (interaction p = 0.005; events 23 / 111)	2.54 (95% CI 1.27–5.10)	p = 0.009
Subgroup: Cardiometabolic burden at the index date	One or more (interaction p = 0.005; events 146 / 317)	1.10 (95% CI 0.84–1.44)	p = 0.47
Subgroup: Sex	Women (interaction p = 0.18; events 89 / 207)	1.54 (95% CI 1.12–2.12)	p = 0.007

Analysis	Specification	Hazard ratio (95% CI)	p-value
Subgroup: Sex	Men (interaction p = 0.18; events 80 / 221)	1.26 (95% CI 0.93–1.70)	p = 0.14
Subgroup: Age group at the index date	18–44 (interaction p = 0.006; events 19 / 23)	3.12 (95% CI 1.35–7.25)	p = 0.008
Subgroup: Age group at the index date	45–64 (interaction p = 0.006; events 71 / 137)	1.63 (95% CI 1.14–2.35)	p = 0.008
Subgroup: Age group at the index date	65+ (interaction p = 0.006; events 79 / 268)	1.11 (95% CI 0.81–1.51)	p = 0.52
Subgroup: Free of recorded cardiovascular disease at the index date	Yes (interaction p = 0.06; events 99 / 241)	1.69 (95% CI 1.24–2.31)	p < 0.001
Subgroup: Free of recorded cardiovascular disease at the index date	No (interaction p = 0.06; events 70 / 187)	1.20 (95% CI 0.73–1.98)	p = 0.47

All models use the Model 2 covariates unless the specification states otherwise; subgroup models omit the variable that defines the subgroup, and any covariate that is constant within a stratum. Freedom from recorded cardiovascular disease means that neither ischaemic cardiovascular disease nor atrial fibrillation was recorded at the index date (Supplementary Material S1). The restriction to subjects free of recorded cardiovascular disease and the corresponding subgroup stratum are the same model and are reported in both places for readability. E-values give the minimum strength of association, on the risk-ratio scale, that an unmeasured common cause of exposure and outcome would need with both in order to account for the observed estimate. The E-value for the confidence limit was computed from the unrounded limit (1.125); computed from the limit rounded to 1.12 it is 1.49. Event counts are those among exposed subjects and referents within each subgroup stratum. CI, confidence interval.

The fully adjusted model adding body-mass index and high-density lipoprotein cholesterol after multiple imputation attenuated the association to 1.17 (95% CI 0.93–1.48), with a confidence interval that included the null. Because body-mass index was missing for more than a quarter of subjects and was missing differentially by exposure group, this analysis rests on an assumption about the missingness mechanism that cannot be checked and is reported as a sensitivity analysis rather than as the primary estimate; it nevertheless indicates that a substantial part of the adjusted association is shared with adiposity. An unmeasured common cause would need to be associated with both exposure and outcome by a risk ratio of at least 2.15 to account for the primary estimate, and of at least 1.50 to move its confidence limit to the null.

3.5. Subgroups

Subgroup estimates are shown in Figure 5 and tabulated in Table 4. The association was concentrated in subjects with no cardiometabolic condition recorded at the index date, in whom the hazard ratio was 2.54 (95% CI 1.27–5.10), compared with 1.10 (95% CI 0.84–1.44) in those with one or more (interaction p = 0.005). A similar gradient was seen across age groups, from 3.12 (95% CI 1.35–7.25) in the youngest band and 1.63 (95% CI 1.14–2.35) in the middle band to 1.11 (95% CI 0.81–1.51) in the oldest (interaction p = 0.006). These estimates rest on few events: 23 among exposed subjects and 111 among referents in the subgroup with no recorded condition, and 19 and 23 in the youngest age band (Table 4).

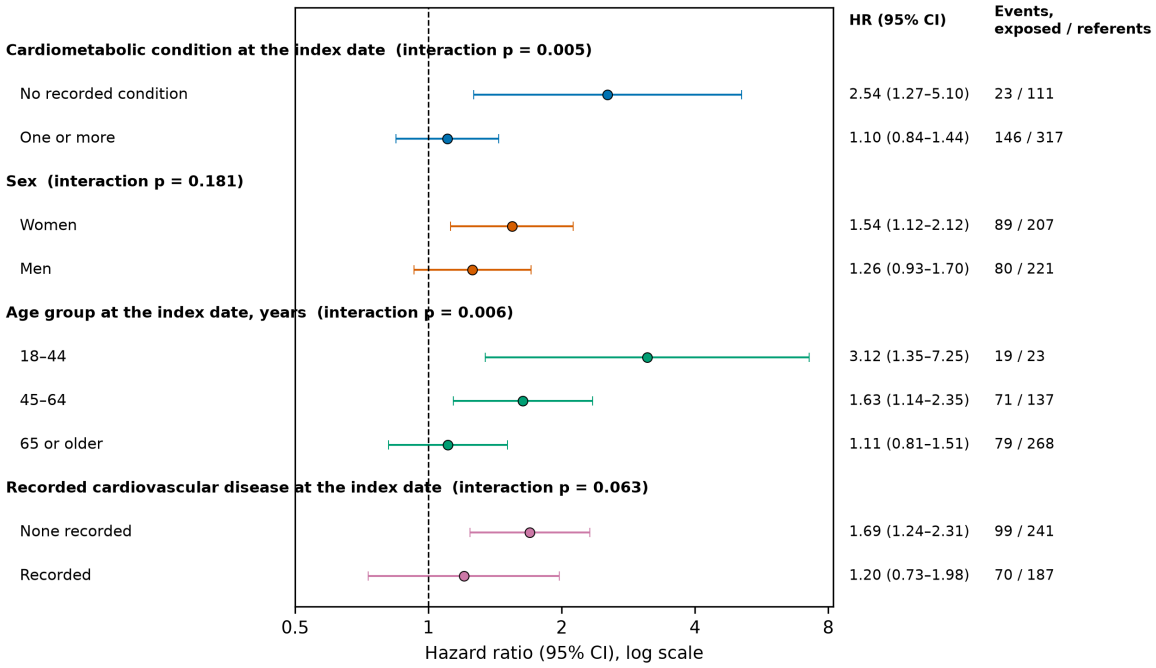


Figure 5. Hazard ratios for a first heart-failure record within subgroups defined at the index date.

Each model is stratified by matched set and adjusted for the index-date cardiometabolic conditions not used to define the subgroup. Interaction p-values are likelihood-ratio tests and appear in Table 4. The right-hand column gives the number of heart-failure events among exposed subjects and referents in each subgroup. HR, hazard ratio; CI, confidence interval.

Estimates in women (1.54 (95% CI 1.12–2.12)) and men (1.26 (95% CI 0.93–1.70)) were similar, with an interaction p value of p = 0.18. Subjects free of any recorded cardiovascular disease at the index date had a larger estimate (1.69 (95% CI 1.24–2.31)) than those with such a record (1.20 (95% CI 0.73–1.98)), with an interaction p value of p = 0.06.

4. Discussion

In this matched community cohort, a first recorded diagnosis of nonalcoholic fatty liver disease was associated with a moderately higher rate of subsequently recorded heart failure, and the excess in absolute terms amounted to about two percentage points of ten-year cumulative incidence once death before heart failure was treated as a competing event. Atrial fibrillation showed no association once conditions present at the index date were taken into account, and ischaemic cardiovascular events showed an association of similar magnitude to that reported in larger cohorts. The relative association for heart failure appeared larger in younger subjects and in those with no cardiometabolic condition recorded at the index date, although these subgroup estimates rest on few events, and it was attenuated towards the null when body-mass index was added to the model.

The heart-failure estimate is smaller than the adjusted hazard ratio of 1.75 reported in a nationwide histology-based cohort with more than ten thousand exposed subjects [3], which is unsurprising: histological confirmation identifies a population with more advanced disease than a diagnosis recorded opportunistically in routine care, and severity gradients within this condition are well described [3]. It sits close to the pooled relative risk of about 1.4 reported for heart failure in a meta-analysis of twelve cohorts [9]. The null association with atrial fibrillation after adjustment differs from the pooled estimate of about 1.4 in the same meta-analysis [9] and from a large study of young adults [10], but is consistent with the

observation that the crude association with atrial fibrillation is largely explained by co-existing cardiometabolic conditions, the pooled estimate falling to 1.19 once these are accounted for [8]. Our matched design already removes age and sex, and our adjustment then removes recorded diabetes, hypertension and dyslipidaemia, so the residual estimate is close to what that literature would predict.

The observation that the relative association was larger among subjects with no cardiometabolic condition recorded at the index date reproduces, for heart failure, the pattern the source report of this cohort described for cardiovascular events generally [2]. Two readings are compatible with the data. The first is biological: in the absence of overt metabolic disease, hepatic steatosis may mark an early stage of the same process and thus carry information that is otherwise unavailable, whereas in adults who already have diabetes and hypertension it adds little to what those diagnoses already convey. The second is arithmetical: the background rate of heart failure is much lower in metabolically unremarkable and younger adults, so the same absolute excess produces a larger ratio. Our data cannot separate these readings. The subgroup estimate rests on 23 events among exposed subjects, its confidence interval is wide, and four subgroup variables were examined, so an interaction of this size could arise by chance; the observation should be regarded as hypothesis-generating rather than as evidence of a different effect in metabolically unremarkable adults.

Two features of the design deserve emphasis because they are uncommon in this literature. Modelling death as a competing event rather than censoring it matters here because exposed subjects died appreciably more often, and an analysis that censored those deaths would attribute to survivors a probability of heart failure that the group as a whole never experienced; the sub-distribution estimate was accordingly closer to the null than the outcome-specific one, and reporting both is now recommended practice in clinical and cardiovascular research [13,18]. Preserving the matched-set stratification also matters: the estimate obtained after discarding the matching was appreciably smaller than the stratified one, which is expected because the two specifications target different quantities, one conditional on the matched set and one marginal, and hazard ratios are not collapsible across such strata; studies that match at design and then fit unstratified models should therefore say which of the two they intend.

This study has several limitations. Diagnoses were those recorded in routine care without central adjudication, so both exposure and outcomes may be misclassified; a diagnosis of fatty liver disease also requires an imaging or laboratory encounter, so exposed subjects have more opportunity for cardiac outcomes to be detected, and this detection pathway would bias the estimate away from the null. The positive-comparator diabetes outcome and the twelve-month exclusion make gross detection artefact less likely as a complete explanation but cannot exclude it, and the earlier analysis of this cohort found that adjustment for a surrogate of access to care did not remove its ischaemic associations [7]. Body-mass index was missing for more than a quarter of subjects and differentially so, which is why it was excluded from the primary model; the multiply imputed model that includes it is the analysis most likely to reflect confounding by adiposity, and its attenuation towards the null should temper any claim of an independent association. Race, ethnicity, alcohol intake, medication and socioeconomic position are not available in the released data, so residual confounding cannot be excluded, although the E-value indicates that an unmeasured factor associated with both exposure and outcome would have to be moderately strong to account for the primary estimate [17]. The released cohort is a ninety per cent random sample of the original, so our counts and estimates will differ slightly from those of the source report [2]. Follow-up ended at last recorded contact, and subjects who left the community would be censored informatively if departure were related to their cardiac risk. Finally, the release carries no information on race, ethnicity or

socioeconomic position, so the composition of the source community cannot be described here, and the community is served by an unusually complete records system; generalisability to more mobile and more diverse populations is therefore uncertain.

For practice, the findings suggest that heart failure deserves a place alongside ischaemic disease among the cardiovascular endpoints considered in adults given this diagnosis, but that the absolute excess over a decade is modest and is shared with the metabolic burden these patients carry. For research, they argue for cohorts that report absolute risk with competing events handled explicitly, that publish the outcome definitions and code, and that examine detection pathways rather than assuming them away; the analysis presented here is reproducible in full from a publicly available dataset, which is not the case for the large registry and electronic-record cohorts that now dominate the field [3,6].

5. Conclusions

In a matched community cohort followed through a complete medical-record-linkage system, a first recorded diagnosis of nonalcoholic fatty liver disease was associated with a moderately higher rate of subsequently recorded heart failure and with an absolute ten-year excess of about two percentage points, whereas no association with atrial fibrillation persisted after adjustment for conditions present at the index date. The relative association appeared larger in younger and metabolically unremarkable adults, on few events, and was attenuated when body-mass index was taken into account, so shared adiposity and differential clinical attention remain plausible explanations and a causal interpretation is not warranted. Cohorts in this field should report absolute risk with death handled as a competing event, since relative estimates alone overstate what a patient can expect.

Declarations

Supplementary Materials: The following supporting information is available: Figure S1, cumulative incidence of atrial fibrillation by exposure group; Figure S2, scaled Schoenfeld residuals for the exposure term of the primary model; Figure S3, cumulative all-cause mortality by exposure group; Figure S4, the directed acyclic graph underlying the adjustment set; Table S1, ten-year and five-year risk differences with independence-based and matched-set bootstrap intervals, and proportional-hazards diagnostics; Supplementary Material S1, analysis code, derived analysis file and a description of the cohort assembly in both public releases.

Funding: This research received no external funding.

Institutional Review Board Statement: As a secondary analysis of publicly available data, the study was exempt from ethics review. The data are de-identified; in them all calendar dates have been replaced by intervals and a random ten per cent of subjects has been withheld. The original cohort was assembled under institutional review board approval at the contributing institutions, as described in the source report [2].

Informed Consent Statement: The analysis used publicly available, de-identified data and no individual could be identified from the released tables.

Data Availability Statement: The three cohort tables analysed here are publicly available in the source archive of the survival analysis package for the R environment (https://cran.r-project.org/package=survival, data sets nafld1, nafld2 and nafld3 as distributed with version 3.8-12), accessed on 1 November 2026. The analysis code and the derived analysis file for the revised analyses are provided as Supplementary Material S1.

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Conflicts of Interest: The authors declare no conflicts of interest.

Author contributions: [Pending: CRediT author contributions and confirmation that all authors approved the final version — to be supplied by the authors]

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Abbreviations and symbols

CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; −, minus.

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