Research Square

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GLP-1 Receptor Agonists and Cardiorenal Outcomes in Non-Obese, Non- Diabetic MASLD: A Propensity Score-Matched Study

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Abstract

Purpose

Non-obese individuals account for up to 30% of metabolic dysfunction-associated steatotic liver disease (MASLD) cases yet are routinely excluded from glucagon-like peptide-1 receptor agonist (GLP-1 RA) outcome trials. Because MASLD is increasingly recognized as the hepatic component of a systemic cardiometabolic disorder, we evaluated the association between sustained GLP-1 RA use and cardiovascular, renal and hepatic outcomes in non-obese, non-diabetic adults with MASLD.

Methods

Using the TriNetX federated health research network, we identified non-obese (body mass index ≤ 27 kg/m²), non-diabetic adults with MASLD and at least one cardiometabolic risk factor. Sustained GLP-1 RA users, defined by a second prescription within three months of an initial prescription started within three months of diagnosis, were matched 1:1 to non-users on 38 demographic, comorbidity, medication and laboratory covariates. Cox models estimated five-year hazard ratios (HR) for major adverse cardiovascular events (MACE), heart failure, major liver outcomes (MALO), acute kidney injury (AKI), and atrial fibrillation/flutter (Afib). Sensitivity analyses excluded baseline metformin, substance use, and tirzepatide.

Results

Among 1,261 matched pairs, sustained GLP-1 RA use was associated with lower rates of MACE (HR 0.54, 95% CI 0.33–0.87), heart failure (0.34, 0.19–0.59), AKI (0.46, 0.26–0.81) and Afib (0.64, 0.42–0.97). MALO did not differ (1.16, 0.59–2.28). Associations persisted after excluding baseline metformin use and were directionally consistent after excluding tirzepatide.

Conclusion

In non-obese, non-diabetic MASLD, sustained GLP-1 RA use was associated with lower cardiovascular and renal event rates but not with hepatic events. These findings support prospective evaluation of GLP-1 RA therapy in this understudied phenotype.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide and is rising in parallel with cardiometabolic disease [1]. Although typically framed as a disease of obesity, a substantial minority of patients, reportedly up to 30%, are non-obese at presentation [2]. This phenotype is not benign as non-obese patients can develop hepatic fibrosis

progression, hepatic decompensation, and adverse cardiovascular and renal outcomes at rates comparable to, if not exceeding, those of obese patients [3,4]. The drivers of disease in the absence of obesity remain incompletely understood, although genetic predisposition, oxidative stress, and altered lipid handling have all been proposed [5]. Despite this, non-obese MASLD remains under-represented in the literature. Importantly, MASLD is increasingly understood as the hepatic manifestation of a systemic cardiometabolic syndrome, thus evaluation of cardiovascular, renal, and hepatic effects is warranted.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have reshaped cardiometabolic care. Beyond glycemic control and weight reduction, they reduce MACE, slow chronic kidney disease progression, and, more recently, have shown histologic benefit in metabolic dysfunction-associated steatohepatitis [6]. These findings suggest that GLP-1 RA benefits extend beyond weight loss and glycemic control and may be mediated by direct vascular, anti-inflammatory, and metabolic mechanisms [7,8]. However, most trials establishing these benefits were conducted in obese patients with cardiometabolic risk factors.

As GLP-1 RA indications broaden, a growing number of non-obese, non-diabetic patients with MASLD are being exposed to these agents. Whether this population derives the cardiovascular, renal, and hepatic protection observed in higher-risk groups is unknown. We therefore conducted a retrospective, propensity score-matched cohort study using the TriNetX federated electronic health record network to evaluate whether sustained GLP-1 RA exposure was associated with reduced rates of MACE, heart failure, acute kidney injury, and Afib in non-obese, non-diabetic adults with MASLD, and additionally examined MALO.

Methods

Data Source and Study Design

We conducted a retrospective cohort study using the TriNetX Research Network, a federated electronic health records (EHR) database comprising 112 participating healthcare organizations across the United States. TriNetX aggregates de-identified patient-level data including diagnoses (ICD-10-CM), medications (RxNorm), procedures (CPT), laboratory values, and demographic characteristics.

Eligibility Criteria

Patients were required to have a diagnosis of non-obese MASLD, defined as the presence of ICD-10-CM code K76.0 (fatty change of liver, not elsewhere classified) or K75.81 (nonalcoholic steatohepatitis), with a recorded BMI of 27 kg/m² or less. To ensure metabolic relevance, all patients were required to have at least one cardiometabolic risk factor documented at or before the index MASLD diagnosis, including essential hypertension (I10), any dyslipidemia (E78.00, E78.01, E78.1, E78.2, E78.4, E78.5), impaired fasting glucose (R73.01), or other abnormal glucose (R73.09). Patients were excluded if they had any diagnosis of diabetes mellitus (E08–E13) at any time, effectively restricting the cohort to non-diabetic individuals. Additional exclusion criteria included alternative etiologies of chronic liver disease (chronic

viral hepatitis B18, alcoholic liver disease K70, autoimmune hepatitis K75.4, primary sclerosing cholangitis K83.01, Wilson's disease E83.01, primary biliary cirrhosis K74.3, hereditary hemochromatosis E83.110, alcohol-related disorders F10, and chronic passive congestion of the liver K76.1), as well as baseline hepatic decompensation (cirrhosis K74.60/K74.69, hepatic failure K72.xx, portal hypertension K76.6, esophageal varices I85.xx, ascites R18), hepatocellular carcinoma (C22.0, C22.8), prior liver transplant (Z94.4), obesity (E66.9), and prior bariatric surgery (CPT 43644, 43645, 43770, 43775, 43842, 43843, 43846, 43847).

Exposure Definition

The exposure cohort comprised patients who initiated a GLP-1 receptor agonist (semaglutide, liraglutide, dulaglutide, exenatide, or tirzepatide) within 3 months of their MASLD diagnosis and subsequently received a second prescription for any GLP-1 RA within 3 months of the first, operationalizing sustained use. The comparator cohort included patients meeting all eligibility criteria who had no GLP-1 RA exposure at any time. The full cohort development flow, including sequential exclusions and matched sample sizes, is shown in Fig. 1.

Index Date and Follow-Up

For both cohorts, the index date was the first date on which a patient met the MASLD cohort definition. Follow-up began on the day after the index date and extended up to 5 years.

Propensity Score Matching

To reduce confounding, 1:1 propensity score matching (PSM) was performed between the sustained GLP-1 RA and no-GLP-1 RA cohorts. Matching covariates (Table S1) spanned four domains. Demographics: current age, age at index, sex, race, and ethnicity. Comorbidities: hypertension, dyslipidemia, ischemic heart disease, other heart disease, cerebrovascular disease, chronic kidney disease, depressive episode, major depressive disorder, anxiety and related disorders, and chronic lower respiratory diseases. Medications: antilipemic agents, beta-blockers, ACE inhibitors, angiotensin II receptor blockers, diuretics, oral hypoglycemic agents, platelet aggregation inhibitors, and insulin. Laboratory values: BMI, hemoglobin A1c, alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count, and serum creatinine. Balance was assessed using standardized mean differences (SMD), with SMD < 0.10 considered acceptable.

Outcomes

The primary outcomes were MACE, defined as a composite of acute myocardial infarction (I21), cerebral infarction (I63), and nontraumatic intracerebral hemorrhage (I61); heart failure (I50); acute kidney injury (AKI; N17); and Afib (I48). The secondary outcome was MALO, a composite of incident cirrhosis (K74.60,

K74.69), hepatic failure (K72.xx), portal hypertension (K76.6), esophageal varices (I85.xx), and ascites (R18.0, R18.8). All-cause mortality was also assessed. Outcomes were analyzed from one day after the index event through 5 years of follow-up. Patients were censored at the date of their last recorded fact in the EHR.

Statistical Analysis

For each outcome, we report the risk (proportion of patients with the outcome), risk difference with 95% confidence interval (CI), risk ratio (RR) with 95% CI, and odds ratio (OR) with 95% CI. Time-to-event analysis was performed using the Kaplan–Meier method with log-rank testing, and HR with 95% CIs were estimated using Cox proportional hazards models. The proportional hazards assumption was assessed using the Schoenfeld residuals test as implemented in TriNetX. The assumption was satisfied for heart failure ($p = 0.35$), acute kidney injury ($p = 0.18$) and MALO ($p = 0.85$), but was not satisfied for MACE ($p = 0.003$) or atrial fibrillation/flutter ($p = 0.043$). Statistical significance was defined as $p < 0.05$. Primary results are reported over 5 years of follow-up.

Sensitivity Analyses

Four pre-specified sensitivity analyses were conducted (Tables S2–S5). First, to isolate GLP-1 RA class effects independent of metformin, we excluded patients with any baseline metformin exposure from both cohorts (n = 1,024 per arm after PSM). Second, to assess whether residual confounding from substance use disorders might explain the primary findings, we excluded patients with any baseline substance use disorder diagnosis from both cohorts (n = 1,039 per arm after PSM). Third, to examine GLP-1 RA class effects exclusive of dual GIP/GLP-1 agonism, we repeated the primary analysis after excluding tirzepatide from the exposure definition (n = 609 per arm after PSM). Fourth, to contextualize findings within the broader non-diabetic MASLD population, we removed the BMI restriction of 27 kg/m² and included all non-diabetic MASLD patients regardless of body habitus, applying the same GLP-1 RA exposure and comparator definitions (n = 23,983 per arm after PSM).

Results

Cohort Characteristics

From 121,090 eligible non-exposed and 1,262 exposed (sustained GLP-1 RA) patients meeting criteria, 1:1 propensity score matching produced 1,261 patients per arm (Fig. 1). Matched cohorts had a mean age at index of approximately 52.7 years and were predominantly female (71.2%). After matching, most covariates were well balanced (SMD < 0.10). Residual imbalance persisted for BMI (28.8 ± 4.2 vs 27.4 ± 4.0 kg/m²; SMD 0.351) and, to a lesser degree, for transaminases, with higher ALT (46.7 ± 43.5 vs 38.8 ± 39.9 U/L; SMD 0.189) and AST (35.8 ± 32.2 vs 31.8 ± 26.7 U/L; SMD 0.136) in the exposed arm (Table 1). FIB-4 could not be computed at the patient level because the federated platform returns group-level summary statistics.

Table 1
Baseline characteristics and 5-year clinical outcomes in non-obese, non-diabetic MASLD after 1:1 propensity score matching (N = 1,261 per arm)

Characteristic / Outcome	Sustained GLP-1 RA (n = 1,261)	No GLP-1 RA (n = 1,261)	HR (95% CI) or Std Diff
Baseline characteristics			
Age at index (years), mean ± SD	52.7 ± 12.4	52.9 ± 14.9	0.010
Female, n (%)	898 (71.2%)	902 (71.5%)	0.007
BMI (kg/m²), mean ± SD	28.8 ± 4.2	27.4 ± 4.0	0.351
HbA1c (%), mean ± SD	5.5 ± 0.4	5.5 ± 0.5	0.053
Hypertension, n (%)	672 (53.3%)	649 (51.5%)	0.037
Dyslipidemia, n (%)	976 (77.4%)	998 (79.1%)	0.042
Creatinine (mg/dL), mean ± SD	0.9 ± 4.1	0.9 ± 3.2	0.005
FIB-4 components[c]			
AST (U/L), mean ± SD	35.8 ± 32.2	31.8 ± 26.7	0.136
ALT (U/L), mean ± SD	46.7 ± 43.5	38.8 ± 39.9	0.189
Platelets (×10⁹/L), mean ± SD	265.3 ± 68.8	265.3 ± 75.6	0.001
Clinical outcomes — n (%); HR (95% CI), p-value			
MACE[a]	27 (2.14%)	45 (3.57%)	**0.54 (0.33–0.87) p = 0.010**
Heart failure	17 (1.35%)	46 (3.65%)	**0.34 (0.19–0.59) p < 0.001**
Acute kidney injury	18 (1.43%)	35 (2.78%)	**0.46 (0.26–0.81) p = 0.005**
Atrial fibrillation/flutter	38 (3.01%)	54 (4.28%)	**0.64 (0.42–0.97)**

[a]MACE = major adverse cardiovascular events (acute myocardial infarction, cerebral infarction, nontraumatic intracerebral hemorrhage). [b]MALO = major adverse liver outcomes (cirrhosis, hepatic failure, esophageal varices, portal hypertension, ascites). [c]AST, ALT and platelets are reported as components of the FIB-4 index; FIB-4 could not be computed directly within the TriNetX federated platform, which provides group-level rather than patient-level data. All standardized differences < 0.10 after matching except where noted; AST (0.136), ALT (0.189) and BMI (0.351) approached but did not achieve full balance. Bold hazard ratios are significant at p < 0.05. HR hazard ratio, CI confidence interval, BMI body mass index

Characteristic / Outcome	Sustained GLP-1 RA (n = 1,261)	No GLP-1 RA (n = 1,261)	HR (95% CI) or Std Diff
Baseline characteristics			
			p = 0.033
MALO[b]	19 (1.51%)	15 (1.19%)	1.16 (0.59–2.28) p = 0.67
All-cause mortality	< 10	< 10	Insufficient events

[a]MACE = major adverse cardiovascular events (acute myocardial infarction, cerebral infarction, nontraumatic intracerebral hemorrhage). [b]MALO = major adverse liver outcomes (cirrhosis, hepatic failure, esophageal varices, portal hypertension, ascites). [c]AST, ALT and platelets are reported as components of the FIB-4 index; FIB-4 could not be computed directly within the TriNetX federated platform, which provides group-level rather than patient-level data. All standardized differences < 0.10 after matching except where noted; AST (0.136), ALT (0.189) and BMI (0.351) approached but did not achieve full balance. Bold hazard ratios are significant at p < 0.05. HR hazard ratio, CI confidence interval, BMI body mass index

Over 5 years of follow-up, sustained GLP-1 RA use was associated with significantly lower rates of MACE (2.14% vs 3.57%; HR 0.54, 95% CI 0.33–0.87; p = 0.010), heart failure (1.35% vs 3.65%; HR 0.34, 0.19–0.59; p < 0.001), acute kidney injury (1.43% vs 2.78%; HR 0.46, 0.26–0.81; p = 0.005), and atrial fibrillation or flutter (3.01% vs 4.28%; HR 0.64, 0.42–0.97; p = 0.033) (Table 1, Figs. 2 and 3). These correspond to absolute risk reductions of approximately 1.4% for MACE (number needed to treat [NNT] ≈ 70), 2.3% for heart failure (NNT ≈ 44), 1.4% for AKI (NNT ≈ 74), and 1.3% for atrial fibrillation or flutter (NNT ≈ 79). MALO did not differ significantly between groups (1.51% vs 1.19%; HR 1.16, 0.59–2.28; p = 0.67), and all-cause mortality involved fewer than 10 events per arm.

After excluding patients with baseline metformin exposure (1,024 per arm), reductions in all four cardiorenal endpoints remained significant (MACE HR 0.51; heart failure 0.32; AKI 0.41; atrial fibrillation or flutter 0.61). After excluding patients with substance use disorders (1,039 per arm), the reduction in AKI remained significant (HR 0.49, 0.25–0.96), whereas the MACE and atrial fibrillation or flutter estimates were attenuated and no longer reached significance. In the tirzepatide-excluded analysis (609 per arm), estimates for MACE and AKI remained directionally consistent with benefit but did not reach significance, in keeping with the smaller sample. MALO remained non-significant across all sensitivity analyses. In a broader non-diabetic MASLD cohort without the BMI restriction (23,983 matched pairs), significant reductions were observed across all endpoints, including MALO (HR 0.17, an approximately 83% relative reduction), contrasting with the neutral hepatic result in the non-obese cohort (Table 2).

Table 2
Sensitivity analyses: hazard ratios (95% CI) for five-year outcomes after 1:1 propensity score matching, under sequential exclusions

Outcome	No metformin (n = 1,024)	No substance use (n = 1,039)	Excluding tirzepatide (n = 609)	General non-diabetic MASLD (n = 23,983)
MACE	**0.51 (0.28–0.95)**	0.67 (0.36–1.25)	0.74 (0.36–1.55)	**0.71 (0.63–0.80)**
Heart failure	**0.32 (0.17–0.59)**	NR	NE	**0.73 (0.66–0.81)**
Acute kidney injury	**0.41 (0.20–0.82)**	**0.49 (0.25–0.96)**	0.66 (0.31–1.37)	**0.60 (0.54–0.68)**
Atrial fibrillation/flutter	**0.61 (0.38–0.97)**	0.89 (0.53–1.47)	1.02 (0.56–1.84)	**0.86 (0.77–0.95)**
MALO	1.05 (0.51–2.18)	1.11 (0.53–2.33)	NE	**0.17 (0.13–0.24)**

Values are hazard ratios (95% CI) from Cox proportional hazards models over 5 years; n is per matched arm. Bold indicates a 95% CI excluding 1.0. NR not reported (heart failure was not returned in the substance-use-excluded analysis), NE not estimable owing to fewer than 10 events, MACE major adverse cardiovascular events, MALO major adverse liver outcomes, HR hazard ratio, CI confidence interval

Discussion

In this propensity score-matched cohort of non-obese, non-diabetic adults with MASLD, sustained GLP-1 RA use was associated with substantially lower rates of MACE, heart failure, AKI, and atrial fibrillation or flutter over 5 years, with relative reductions of 46%, 66%, 54%, and 36%, respectively. These associations persisted after excluding patients with baseline metformin exposure and remained directionally consistent after excluding tirzepatide, supporting a GLP-1 RA class effect rather than a single-drug effect [9–11]. To our knowledge, this is among the first analyses to examine non-obese, non-diabetic patients on sustained GLP-1 RA therapy, a group to whom the conventional indications of weight loss and glycemic control are least applicable, yet in whom a cardiovascular and renal association is nonetheless observed.

The cardiovascular and renal pattern we observed is consistent with existing evidence that GLP-1 RA benefit extends beyond glycemic control and weight reduction [12,13]. In the SELECT trial, semaglutide reduced MACE in overweight and obese adults without diabetes to a degree not fully explained by weight loss [11]. Proposed mechanisms include reduced vascular inflammation and improved endothelial function, slowing of atherosclerotic plaque progression, natriuresis with modest blood pressure lowering, and improved cardiac loading and myocardial function [9,11,13]. The renal association in our study is concordant with the FLOW trial, in which semaglutide slowed kidney function decline through both hemodynamic and anti-inflammatory pathways [12]. Our findings extend these observations to a

population in which obesity and hyperglycemia are absent, suggesting that the cardiorenal signal is difficult to attribute to weight loss or glycemic improvement and may instead reflect more direct, pleiotropic drug effects. Framed against the systemic view of MASLD outlined above, these are not incidental extrahepatic findings but observations about what may be the dominant source of morbidity in the non-obese, non-diabetic MASLD population, in a phenotype that prior trials have excluded.

In contrast, MALO did not differ significantly in the non-obese cohort (HR 1.16), diverging sharply from the approximately 83% RR observed in the broader, all-BMI non-diabetic cohort. We interpret this contrast cautiously, for several reasons. First, hepatic events were rare in both groups (19 in the sustained GLP-1 RA arm versus 15 in the no-GLP-1 RA arm), leaving the comparison underpowered. Second, despite matching, the exposed arm had higher baseline aminotransferases, indicating potentially more active liver disease at the time of therapy initiation and biasing the estimate against benefit. Third, non-obese patients generally have a lower baseline burden of fibrosis, so a healthy-patient bias may reduce the frequency of follow-up and fibrosis screening. Fourth, non-obese MASLD is increasingly understood as genetically distinct, driven less by degree of adiposity than by genetic determinants such as PNPLA3 and TM6SF2 variants together with altered lipid handling [5,14,15]. This potentially suggests that the hepatic and the cardiometabolic components of MASLD may respond to GLP-1 RA exposure on different timescales, or through different mechanisms, in patients whose disease is not adiposity-driven.

Our study has several limitations. Because the exposure definition required a confirmatory prescription after the index date, a patient had to remain event-free long enough to qualify as a sustained GLP-1 RA user while follow-up had already begun. This immortal-time bias can shift estimates toward an apparent benefit, and future landmark analyses would address this limitation. Relatedly, the proportional hazards assumption was not satisfied for MACE or atrial fibrillation/flutter, indicating that the association with these outcomes varied across follow-up; the corresponding hazard ratios should therefore be interpreted as time-averaged summaries rather than a constant effect, whereas estimates for heart failure, acute kidney injury and MALO, for which the assumption held, are not subject to this caveat. Non-proportionality of this direction is an anticipated consequence of the sustained-exposure definition, which suppresses early events in the exposed arm, and these two limitations are best considered together. In addition, sustained GLP-1 RA users may differ from non-users in health-seeking behavior and adherence in ways that diagnostic coding cannot capture. We mitigated this by matching on medication classes and comorbidities and through the substance-use sensitivity analysis. More broadly, as an observational study reliant on coded data, residual confounding from unmeasured factors such as diet, physical activity, and fibrosis stage remains possible; to reduce this, we matched on 38 demographic, comorbidity, medication, and laboratory covariates and achieved acceptable balance for most. The non-obese cohort relied on coded BMI ≤ 27 kg/m² recorded at any time, and BMI remained imbalanced after matching (SMD 0.351). This is an intrinsic constraint of the design, since BMI serves simultaneously as an eligibility criterion and a matching covariate, making complete balance on a cohort-defining variable difficult to achieve. Because this population falls outside the primary indications for GLP-1 RA therapy, the indication for treatment could not be obtained from coded data and remains a potential confounder. Similarly, MASLD diagnosis, cardiometabolic risk factors, comorbidities, and medication exposures such

as metformin relied on ICD-10 codes without an established temporal relationship. Outcome events were likewise defined by diagnosis codes, and the number of events, particularly MALO, was limited, potentially obscuring true associations. Furthermore, associations derived from a federated database may reflect relationships captured only at specific coded time points. Finally, the renal endpoint was limited to acute kidney injury; incident and chronic kidney disease were not evaluated.

Further investigation through both retrospective and prospective studies in non-obese MASLD patients on GLP-1 RA therapy is warranted to confirm these associations. As an initial step, a retrospective study at a large single-center institution with confirmed MASLD, verified medication use, and follow-up anchored to the time of confirmed exposure would mitigate the immortal-time bias inherent to database analyses. This could be followed by a prospective cohort enrolling non-obese, non-diabetic MASLD patients at the time of GLP-1 RA initiation, with longitudinal cardiovascular, renal, and hepatic monitoring to establish temporality and capture chronic endpoints. A multicenter design capturing diverse populations and cardiometabolic subtypes would further validate these findings and improve generalizability.

Our study highlights the potential cardiovascular and renal association of sustained GLP-1 RA use in non-obese, non-diabetic adults with MASLD, a population long excluded from previous trials. These associations were consistent across primary and sensitivity analyses, even after 1:1 propensity score matching, exclusion of baseline metformin use, and exclusion of tirzepatide use. However, liver related outcomes did not differ significantly. Our findings suggest that the cardiometabolic effects of GLP-1 RA may extend beyond the focus of obesity or diabetes to benefit non-obese MASLD phenotypes. Prospectively, this special population deserves adequately powered studies to confirm these associations and design risk-reduction strategies.

Declarations

Competing Interests

The authors have no relevant financial or non-financial interests to disclose. Anh Thu Nguyen, Yahya Haj Hamad, Riddhi Prateek, Daanish Imam, Harish Gopalakrishna, and Gurinder Luthra declare no conflicts of interest.

Ethics Approval

This study used de-identified, aggregated patient data from the TriNetX federated health research network. Because the data contain no protected health information and cannot be linked to individual patients, this study does not constitute human-subjects research and did not require Institutional Review Board review or approval. All procedures were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. This article does not contain any studies with animal subjects performed by any of the authors.

Consent to Participate

Because the data are de-identified and aggregated, the requirement for informed consent was waived, and no individual patient identifying information is included in this article.

Consent to Publish

No individually identifiable patient data are reported; consent to publish is therefore not applicable.

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Author Contribution

A.T.N., H.G., Y.H.H., R.P. and D.I. conceived and designed the study. A.T.N. and Y.H.H. collected and assembled the data and performed the data analysis and interpretation. A.T.N., H.G. and G.L. provided administrative support. A.T.N. prepared the figures and tables. All authors contributed to writing the manuscript, reviewed it critically, and approved the final version.

Data Availability

The data supporting the findings of this study were accessed through the TriNetX Research Network and are not publicly available. TriNetX data are available to qualified researchers affiliated with participating healthcare organizations under a data use agreement with TriNetX, LLC (https://trinetx.com); the authors received no special access privileges. Cohort definitions, ICD-10-CM, CPT and RxNorm code lists, and the aggregate analytic output underlying all reported results are available from the corresponding author upon reasonable request.

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Figures

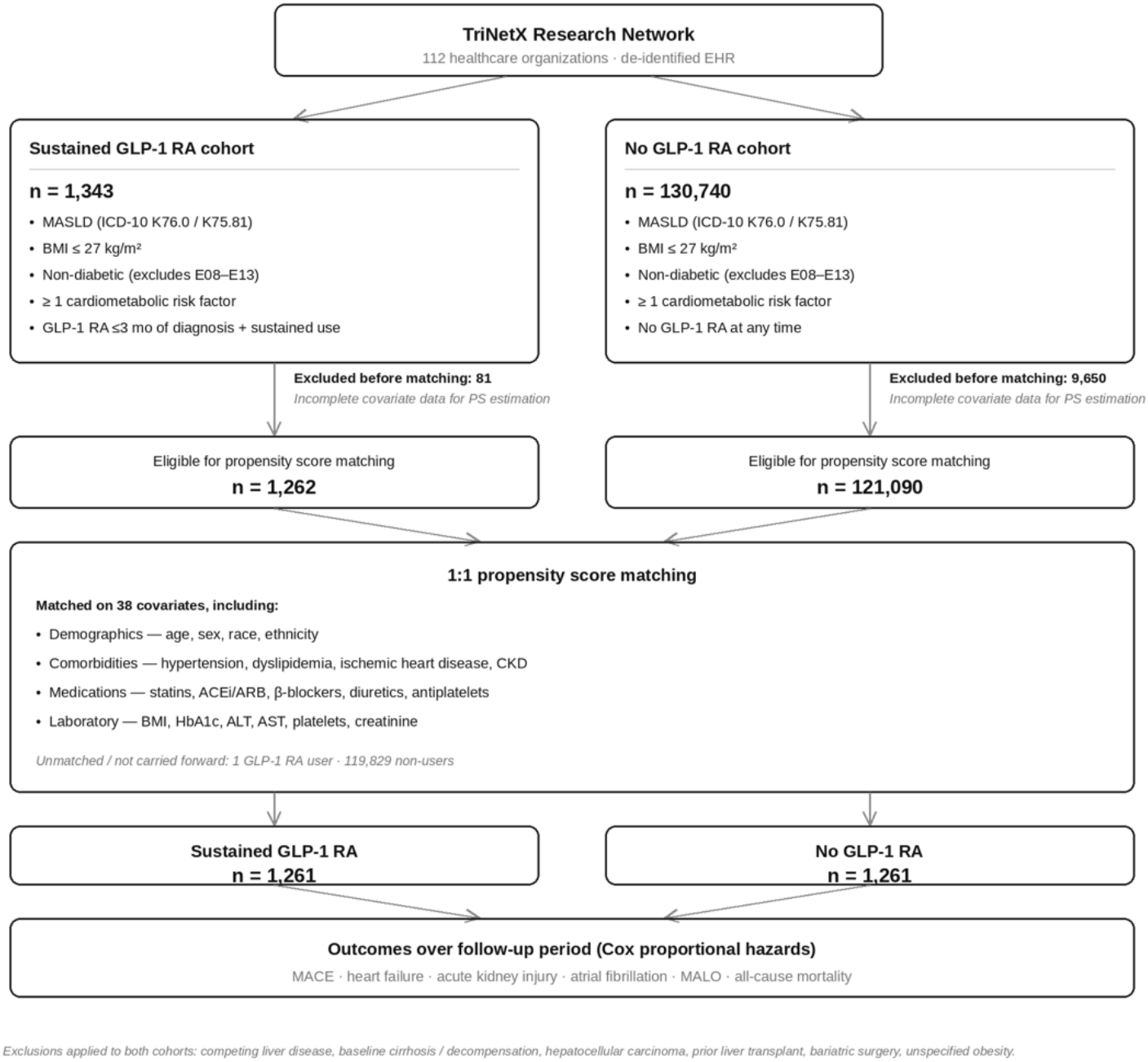


Figure 1

Cohort derivation flow chart outlining sequential exclusions and matched sample sizes

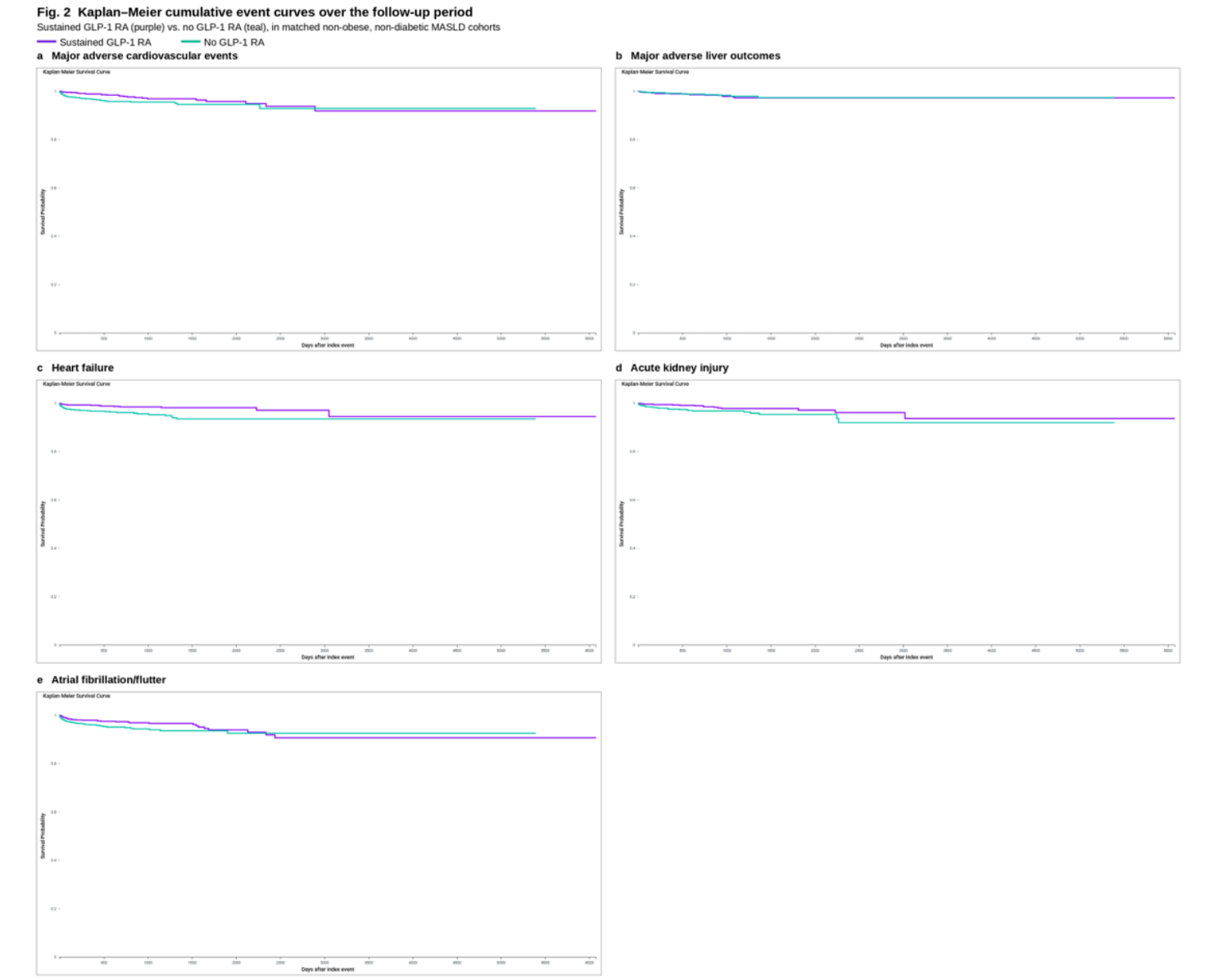


Figure 2

Kaplan–Meier cumulative event curves over five years of follow-up. Panels show (a) major adverse cardiovascular events, (b) heart failure, (c) acute kidney injury, (d) atrial fibrillation/flutter, and (e) major adverse liver outcomes. Hazard ratios with 95% confidence intervals were derived from Cox proportional hazards models

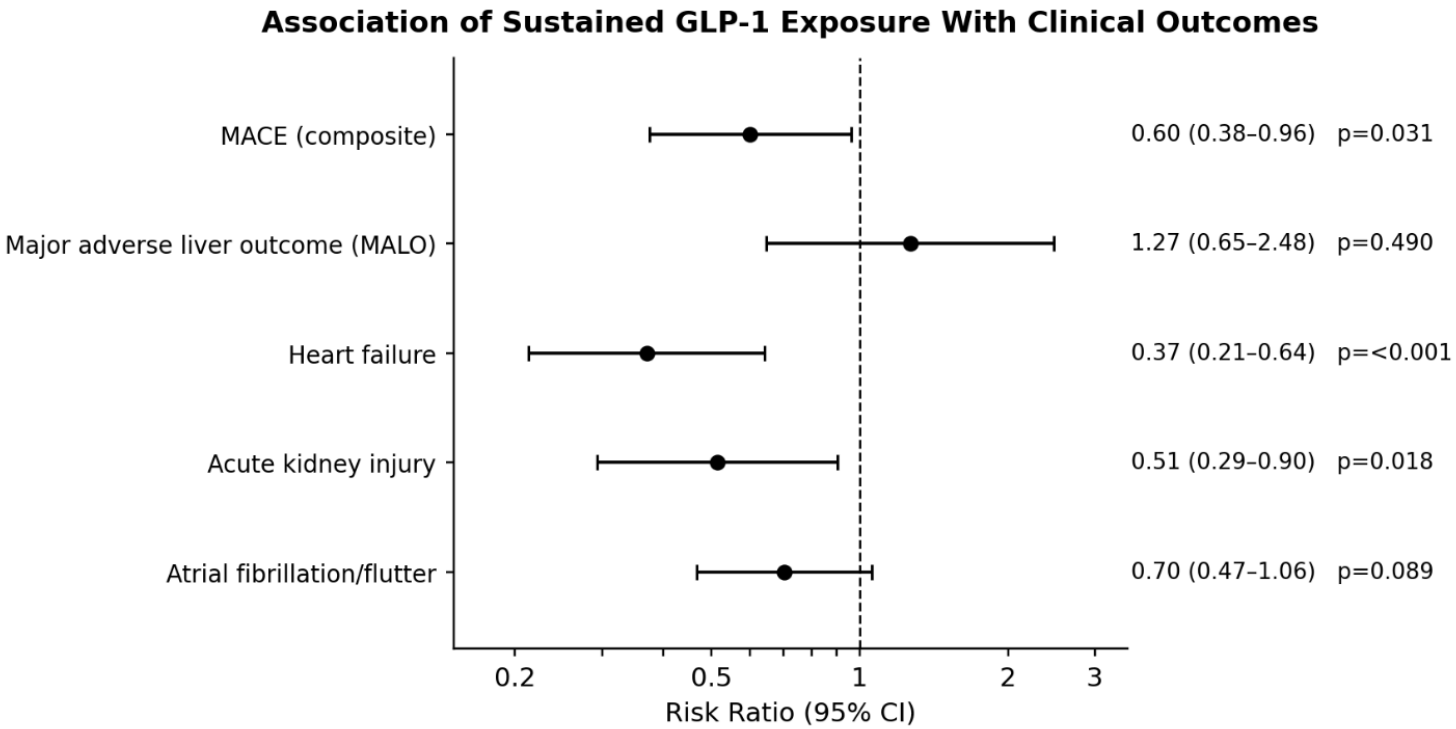


Figure 3

Forest plot of hazard ratios for five-year outcomes in the primary matched cohort. Squares denote point estimates and horizontal lines the 95% confidence intervals; the filled squares indicate statistically significant reductions and the open square the non-significant liver outcome. A hazard ratio below 1.0 (left of the dashed reference line) favors GLP-1 RA use. MACE, major adverse cardiovascular events; MALO, major adverse liver outcomes